A GENERAL SYNTHESIS OF THE ACARNIDINES

A thesis

submitted in partial fulfilment

of the requirements for the Degree

of

Doctor of Philosophy

in the

University of Canterbury

by

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University of Canterbury

1982

ACKNOWLEDGEMENTS

I wish to express my extreme indebtedness to my supervisors, Dr. John W. Blunt and Dr. Murray H.G. Munro, for their support and guidance.

Special thanks are extended to my wife, Sue, my parents and the outlaws, without whom this thesis could not have been completed.

I am also grateful to Professor K.L. Rinehart Jr., University of Illinois, Urbana, U.S.A., for n.m.r. and mass spectral data on the acarnidine natural products and for coordinating the bioassays. Dr. J. Carter Cook, University of Illinois, recorded the f.a.b. mass spectra of the synthetic acarnidines.

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ABSTRACT

A general synthetic route to the acarnidines (1) is described. The acarnidines (1) were isolated from the marine sponge *Acarnus erithacus* and were reported[7] to possess antimicrobial activity and modest antiviral activity. Twenty-one acarnidines and analogues have been prepared so that structure-activity comparisons could be made.

Although there are several reported methods for assembling acyclic triamines and amidoalkylguanidines the synthesis of derivatives in this work has been restricted by a lack of sensitivity, forcing conditions or because bis-products were formed. To overcome these problems a convergent synthetic strategy has been developed which made use of monoprotected diamines. Reductive alkylation of the amines led to acyl triamines which could be further selectively acylated and amidinated to form the acarnidines.

Many other synthetic methods that were attempted, but failed, are also described.

CHAPTER I

INTRODUCTION

1. GENERAL INTRODUCTION

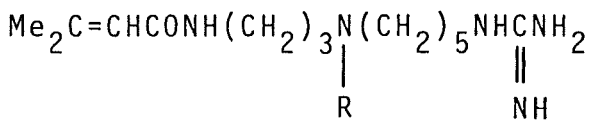
Along with his earliest awareness, man has exploited the environment to promote his wellbeing and survival. In association with magic and religion there has been an historical use of folk medicine to combat disease and alleviate pain. The earliest recorded writings of remedies also noted that some plant species were toxic and animal species venomous. There was a universal interest in poisons and antidotes and a variety of marine toxins were known and documented[1,2]. Marine biology was used to a limited extent in the treatment of various diseases.

The early toxicological observations of the marine world are continually being substantiated today; however, compared to the extensive developments of the terrestrial resources, the marine environment has yielded only a small number of useful biologically active compounds. Effort is now being expended to increase our knowledge of the biological activity of marine organisms in screening programs conducted around the world.

The oceans hold a great deal of potential for the discovery of a large number of chemicals suitable for exploitation, as about eighty percent of the earth's biology exists in the marine world[3]. Biologically active compounds have been isolated from all forms of ocean life[4,5].

The nature of the oceans creates problems in the study and potential utilization of the marine resource. Aspects of the flux of chemical nutrients and solar radiation provide a nonuniform environment and variations in the activity of extracts of the same species collected at different locations occur. Often organisms are devoid of biological activity in one part of the ocean whereas the same species may synthesize or assimilate potent toxins in other areas. Seasonal and growth variations are also significant as the ecology of inter-species competition contributes to the synthesis of many diverse biologically active compounds. The analysts' difficulties extend beyond the problems of identifying biological activity in marine organisms, as many compounds rapidly decompose during isolation.

In a contribution to the screening of marine organisms and the identification of the biologically active components, a shipboard survey of the flora and fauna of the Gulf of California was undertaken[6]. Among the biologically active compounds identified was a new class of guanidino compounds, the "acarnidines" (1a-c), that were isolated from the red-orange sponge *Acarnus erithacus* (de Laubenfels)[7]. The acarnidines have in common a substituted homospermidine skeleton and differ in the fatty acid substituent, R.



(1 a-c)

1a, R = - $CO(CH_2)_{10}CH_3$

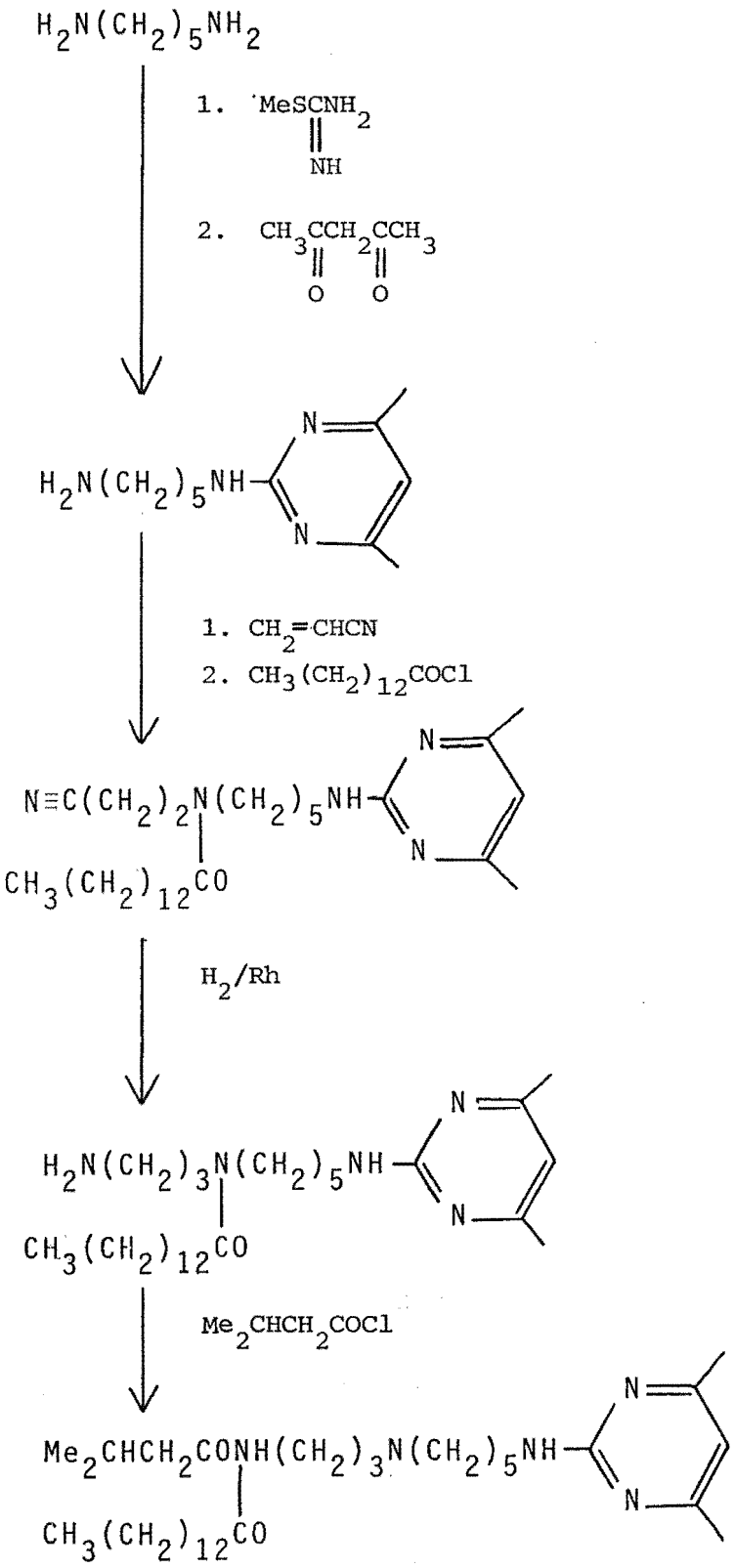
1b, R = - $CO(CH_2)_3CH{=}CH(CH_2)_5CH_3$ (Z)

1c, R = - $CO(CH_2)_2CH{=}CH(CH_2)_2CH{=}CHCH_2CH{=}CHCH_2CH_3$ (all Z)

The acarnidines (1) were reported to possess anti-viral activity against *Herpes simplex*, type I, cytotoxicity against L1210, and KB (ED_{50} < 10 μg ml^{-1}) tumour cells and CV-1 (monkey kidney) cells as well as broad antimicrobial activity. The structures were elucidated by mass spectrometry, ^{13}C- and ^{1}H n.m.r., and degradative methods. The dimethylpyrimidinyl derivative of acarnidine (1a) was also prepared and compared to the pyrimidinyl analogue (2) prepared according to Scheme I.

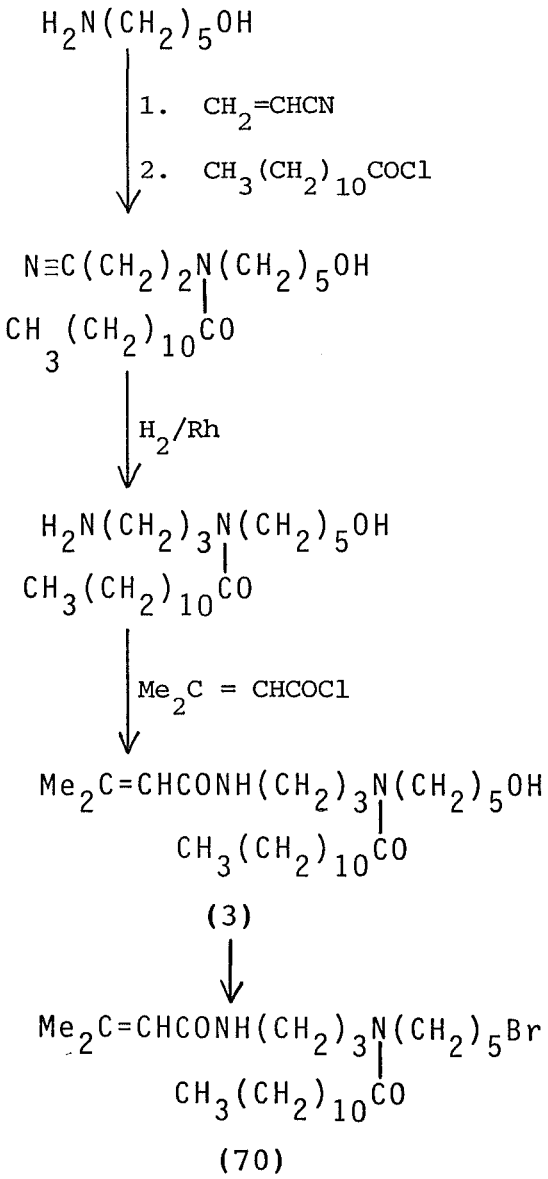
In an unsuccessful attempt to prepare the natural product (1a), Gottschalk prepared the deguanidino-alcohol derivative (3) according to Scheme II[8].

The alcohol (3) and pyrimidinyl derivatives of the acarnidine mixture (1) were tested for biological activity against four microorganisms, but they were found to be relatively inactive compared to the mixture of the natural products (1a-c).


H2N(CH2)5NH2
1. MeSCNH2 (NH)
2. CH3CCH2CCH3 (O O)
H2N(CH2)5NH
1. CH2=CHCN
2. CH3(CH2)12COCl
N≡C(CH2)2N(CH2)5NH
CH3(CH2)12CO
H2/Rh
H2N(CH2)3N(CH2)5NH
CH3(CH2)12CO
Me2CHCH2COCl
Me2CHCH2CONH(CH2)3N(CH2)5NH
CH3(CH2)12CO

(2)

SCHEME I

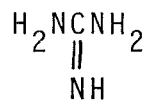

H2N(CH2)5OH
1. CH2=CHCN
2. CH3(CH2)10COCl
N≡C(CH2)2N(CH2)5OH
CH3(CH2)10CO
H2/Rh
H2N(CH2)3N(CH2)5OH
CH3(CH2)10CO
Me2C = CHCOCl
Me2C=CHCONH(CH2)3N(CH2)5OH
CH3(CH2)10CO
(3)
Me2C=CHCONH(CH2)3N(CH2)5Br
CH3(CH2)10CO
(70)

SCHEME II

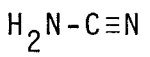
2. THE CHEMISTRY AND BIOLOGICAL ACTIVITY OF GUANIDINES

It is not surprising that the potency of the acarnidines (1) is centred upon the guanidino group.* The ionic nature of guanidine (4) at physiological pH enables it to pass freely through aqueous biological systems, yet with suitable nonpolar substituents, it can reach most hydrophobic locations where biological activity is desired.

Guanidine (4) and monoalkylated guanidines are among the strongest known organic bases forming stable salts with weak acids (pK_a 13.4-13.9). Free guanidines are thermally labile and may dissociate to ammonia or primary amines and cyanamide (5), or if concentrated may oligomerize, for example to dicyanodiamide (6)[9].



(4)



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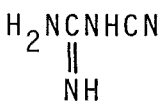

(6)

The increased stability of symmetrically planar guanidinium ions is reflected in the high base strength. Most of the positive charge is located in the vicinity of the central carbon atom. The guanidinium ion is of a similar size to the hydrated sodium ion $[Na(OH_2)_3]^+$ and appears to be a factor in the biological activity of guanidinium compounds[10]. Alkylation of the guanidinium ion would create a "drag" compared to the normal movement

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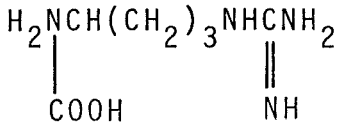
* For convenience, guanidino compounds are formulated in the unprotonated form.

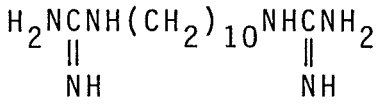
in physiological systems thus interfering with the sodium function. The guanidinium ion is a weaker nucleophile than the amines and accordingly is less reactive as well as being difficult to reduce.

The guanidino function is ubiquitous to all forms of life as it is a substituent of one of the "essential" amino acids, arginine (7).



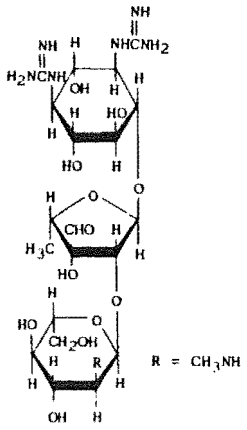
(7)

Guanidines have been studied for many years as a possible source of medically useful compounds. Over fifty-five years ago the chemical synthalin (8) was used briefly as a hypoglycaemic drug which led to studies of guanidino compounds as insulin substitutes. It is also bacteriocidal.



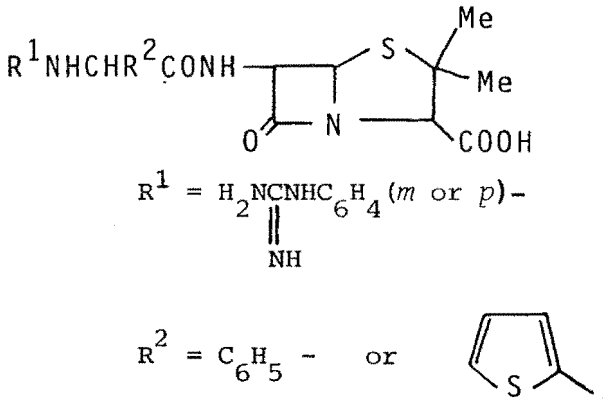
(8)

The first compound effective in the treatment of tuberculosis, streptomycin (9), was a diguanidino compound isolated from the culture of *Streptomyces griseus*.



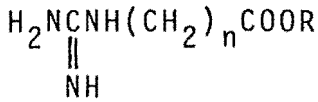
(9)

Derivatization of the guanidino groups of streptomycin (9) caused a decrease in its bacteriocidal properties while increasing its toxicity. Other antibiotics have been synthetically modified to incorporate the guanidino group, for example the penicillins (10).



(10)

Guanidino fatty acids were also shown to be bacteriocidal compounds.

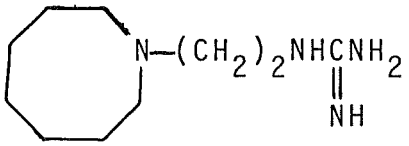


(a) n = 1 - 5; R = H

(b) n = 2 - 8; R = C_7 - C_{12}

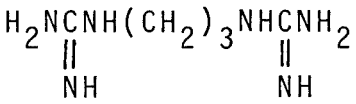
(11)

Another stimulus for extensive research into the medicinal use of guanidino compounds was the discovery of the potent hypotensive properties of guanethidine (12).



(12)

Some synthetic guanidino compounds have also been reported to possess antitumour activity [e.g. (13) and (14)] and antimalarial properties [e.g. (15) and (16)].



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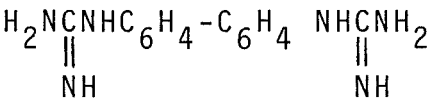

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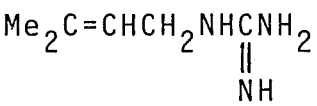
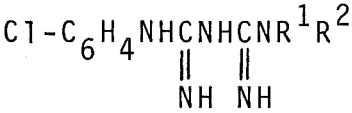


(15)

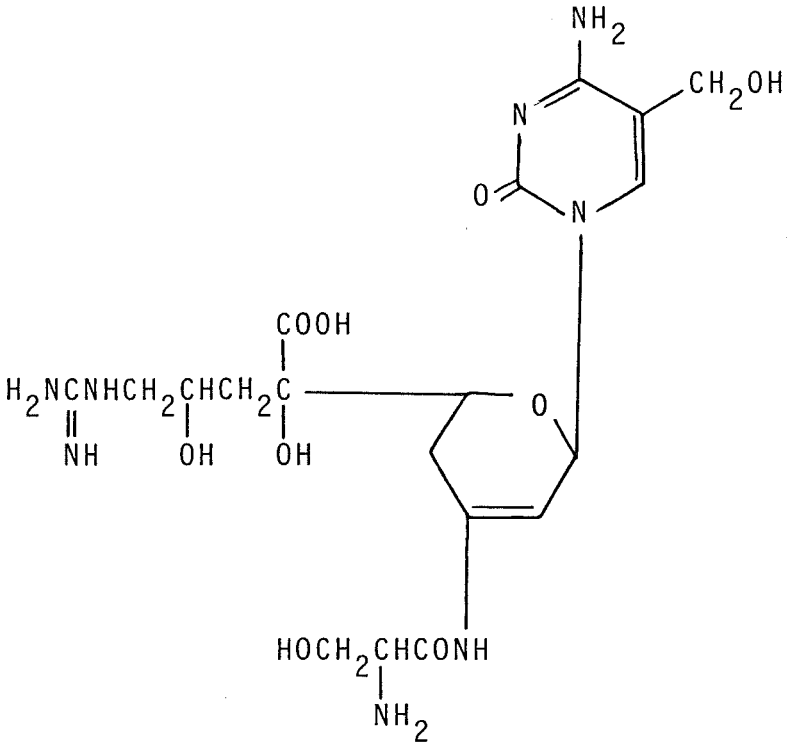


R^1 and R^2 are short alkyl chains.

(16)

Agricultural usage of guanidino compounds (for example N,N-dialkyl-N'-arylguanidines) is becoming common in the control of mildews, rusts, scab and fruit tree pests[8]. Most of the guanidino compounds from a non-marine source are isolated from microorganisms, for example the recently isolated compound mildiomycin (17), which possesses potent activity against powdery mildew yet possessing a very low toxicity to fish and mammals, was isolated from a

Streptoverticillium culture[11].

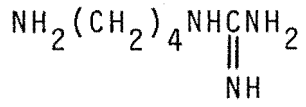


(17)

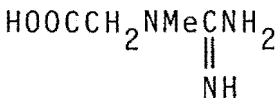
3. MARINE GUANIDINE COMPOUNDS

Although unusual guanidino compounds have been isolated from cultures, many more compounds with unique structures have been isolated from marine sources. A review of marine guanidine compounds has recently been published[12], thus the following discussion is only an updated summary of marine guanidine compounds. Peptidic guanidino compounds are not included.

The most widely distributed guanidines apart from arginine (7) are agmatine (18) and creatine (19). They all possess



(18)

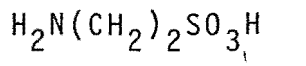


(19)

a function related to energy transfer in muscle tissue, creatine (19) being dominant in the vertebrates. Agmatine (18) also is a metabolite of arginine (7).

Although the simple linear guanidines are widely distributed in nature, the greatest diversity is found in marine worms. Hydroxylated arginines are often found in the seeds of higher plants and less often in marine organisms although this could be a result of a lack of research in the marine chemistry. Amine substituted agmatines are common to molluscs and crustaceans and various N-alkyl and N-acyl compounds have been isolated. Various ω-guanidinoalkylcarboxylic acids have also been isolated from a variety of marine invertebrates.

All of the sulphur-containing guanidine compounds are derived from the commonly encountered aminosulphonic acid, taurine (20). Asterbin (21), found in starfish, is one of the rare acyclic guanidino compounds substituted on two nitrogen atoms.



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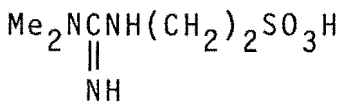
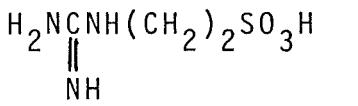


(21)

Taurocyamine (22) is widely distributed among the invertebrates and is often found in smaller concentrations in the vertebrates. Hypotaurocyamine (23) is also found and is

biosynthesized by transamidination between arginine (7) and the amine. Taurocyamine (22) is a product of oxidation of hypotaurocyamine (23).



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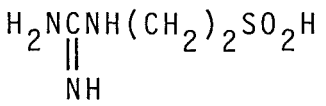
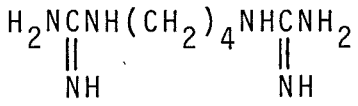


(23)

Two of the three known natural diguanidines, arcaine (24) and audouine (25), are from marine invertebrates. The third diguanidine, hirudonine (26), is only found in terrestrial and fresh water worms.



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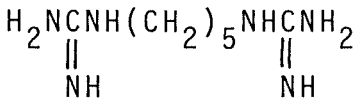

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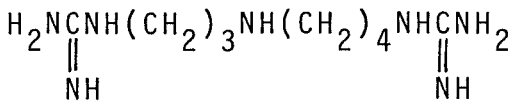

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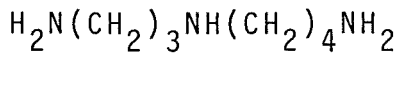
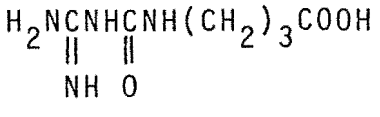


(27)

The three diguanidines have been shown to be biosynthesized by transamidination from arginine (7) to the respective diaminoalkanes and to the triamine, spermidine (27).

Two unusual metabolites (28) and (29) have been isolated from a species of red alga.



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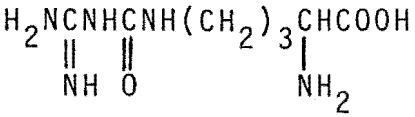
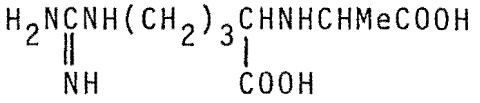


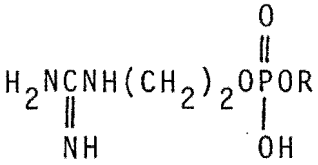
(29)

Octopine (30), an arginine derivative, was first isolated from octopus muscle but it has since been found in many molluscs and worms.

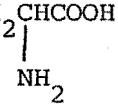


(30)

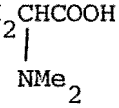
Three compounds (31a-c) derived from the guanidinoethyl phosphate residue are thought to be phosphagen precursors (*vide infra*). They are found in several marine invertebrate species but lombricine (31a) is also found in earthworms.



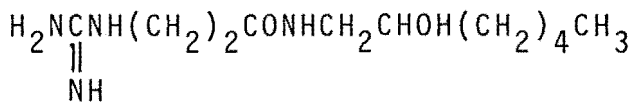
(31a-c)

31a, R = 

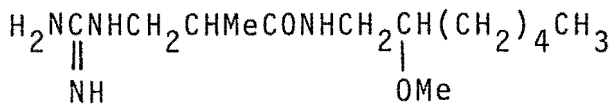
31b, R = - Me

31c, R = 

Phascoline (32) and phascolosomine (33) were found in the viscera rather than the muscle tissue of three species of a marine worm.



(32)



(33)

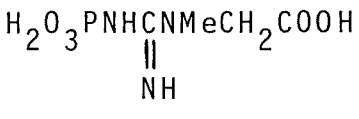
Some of the above compounds have been deduced to be phosphagen precursors. Phosphagens are an important class of compounds (in vertebrates and invertebrates) which are present in very high concentration in muscle tissue where they serve as an energy reserve for ATP synthesis. The important feature of the phosphagens is the "energy-rich" bond between the guanidino and phosphoryl residues. The bond's lability is due to the high resonance stability of each ion following bond cleavage, its function being demonstrated by the following equation.

Phosphagen + ADP $\rightleftharpoons$ guanidine derivative + ATP

Glycolysis and oxidative phosphorylation reactions proceed too slowly for active muscle tissue.

Phosphocreatine (34) is the phosphagen of vertebrates while phosphoarginine (35) is typical of the

invertebrates.



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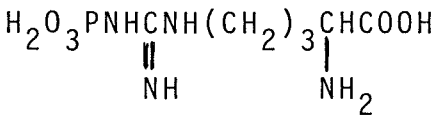
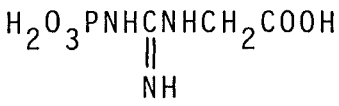


(35)

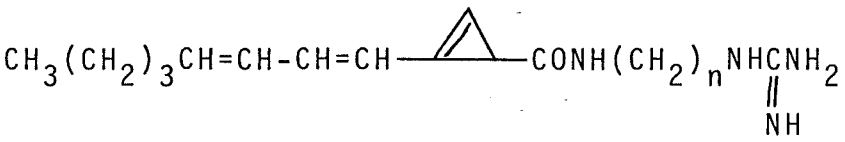
Marine worms account for most of the remaining six known phosphagens. They are phosphoglycocyamine (36) and the phosphorylated analogues of compounds (22), (23) and (31).



(36)

Apart from the acarnidines (1) Rinehart, *et al.* have found two other classes of novel guanidine compounds.

The polyandrocarpidines (37a,b) are fatty acid derivatives similar to the acarnidines (1) yet were isolated from quite a different marine organism, a tunicate.



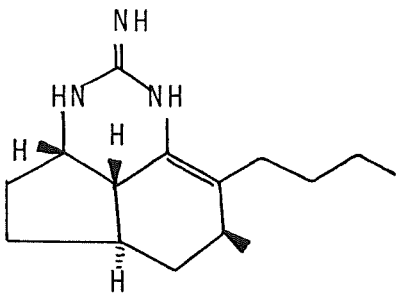
(37a,b)

37a, n = 4

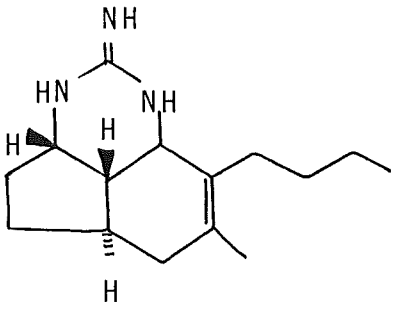
37b, n = 5 .

A feature of the polyandrocarpidines (37) is that they possess the cyclopropenyl ring; a ring that has been encountered only twice before in natural products.

The third class of guanidino compounds isolated by Rinehart's group, from a sponge, are the isomers ptilocaulin (38) and isoptilocaulin (39)[13].



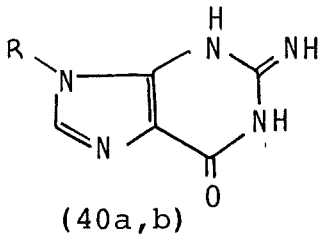
(38)



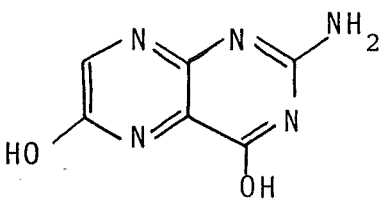
(39)

The guanidines (37-39) are all antimicrobial and cytotoxic, and compounds (37) are antiviral.

Many cyclic natural products incorporate the guanidine function into the ring system. Guanine (40a) guanosine (40b) and xanthopterin (41) are ubiquitous in nature although some nonclassical derivatives have been isolated from marine organisms.



(40a,b)



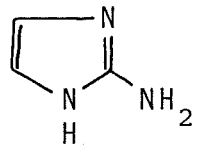
(41)

40a, R = H

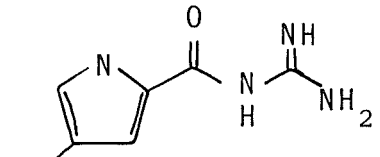
40b, R = ribose

There is a class of compounds isolated from various sponge species which contain a (bromo)pyrrole and a guanidine residue. The simplest compounds are 2-amino-imidazole (42) and N-amidino-4-bromopyrrole-2-carboxamide (43).

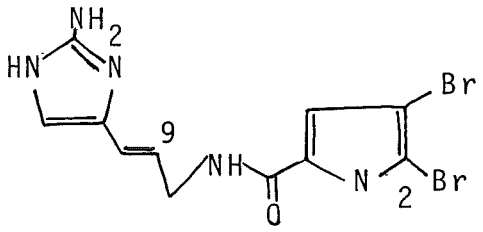
Oroidin (44) and its 2-debromo symmetrical dimer sceptrin (45) (cyclization at Δ^9) have also been isolated. Sceptrin (45) appears not to be an artifact of oroidin (44)[14]. Another group of compounds, the phakellins (46a-c), are very similar to oroidin (44) differing by being cyclized derivates.



(42)



(43)



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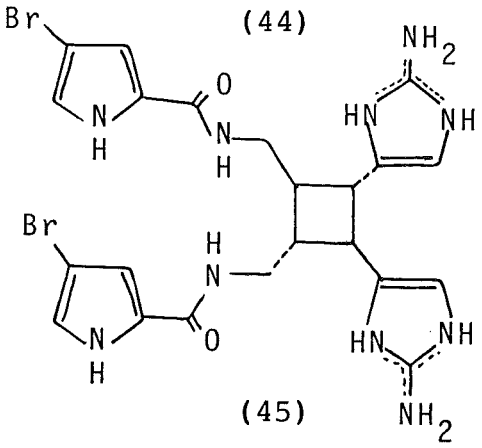

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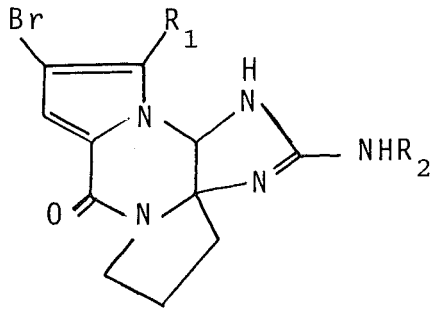


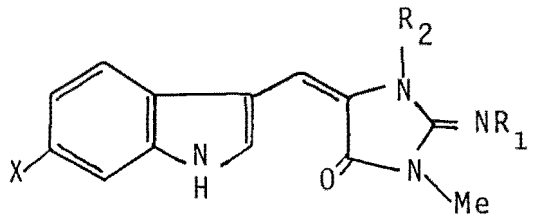
(46)

46a, $R_1=R_2=H$

46b, $R_1=Br$; $R_2=H$

46c, $R_1=Br$; $R_2=-COCH_3$

A class of tetracyclic compounds, the aplysinopsins (47a-d) which also contain the brominated pyrrole have been isolated from a sponge species[12,15].

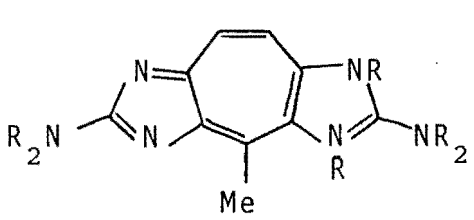


(47a-d)

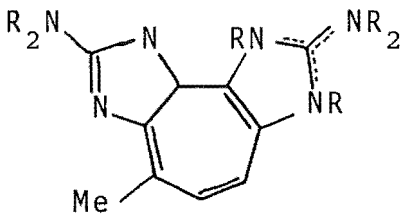
	R_1	R_2	X
47a,	H	Me	H
47b,	Me	Me	H
47c,	H	H	H
47d,	H	H	Br

Aplysinopsin (47a) possesses potent antitumour activity and methylaplysinopsin (47b) has commercial potential as an antidepressant.

Fourteen derivatives of tetraazacyclopent(*f*)-azulene (48) and eleven derivatives of tetraazacyclopent(*e*)-azulene (49) (the zoanthoxanthins) have been isolated from the invertebrate order *Zoanthidea*.



(48)

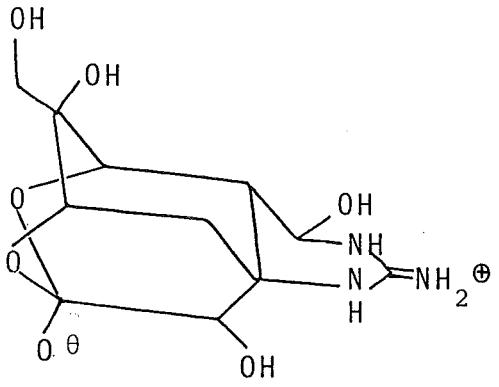


(49)

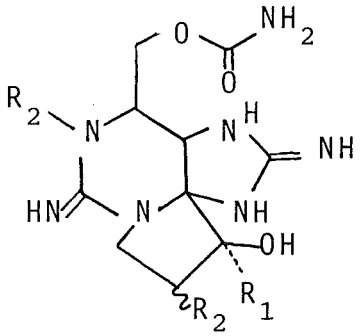
The derivatives vary in the degree of methylation of the R groups although one chloro derivative has also been isolated. They are smooth muscle relaxants and are DNA intercalating agents.

Tetrodotoxin (50) and saxitoxin (51) are two of the most studied of the guanidine-containing marine natural

products as they are potent neurotoxins. Tetrodotoxin (50) is found in several unrelated fish species, an octopus species and in the Costa Rican tree frog.



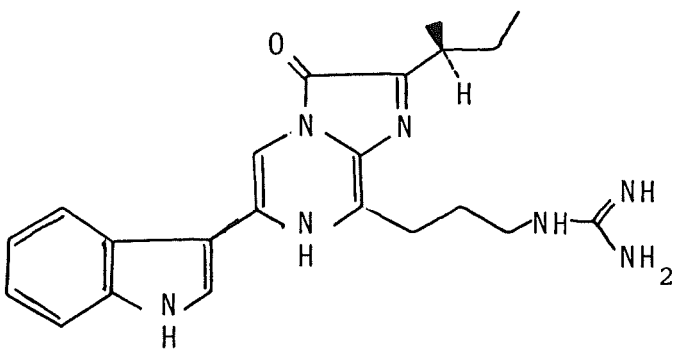
(50)



(51)

Saxitoxin (51)(R_1=OH; R_2=R_3=H) is the main toxin associated with the "red-tide" resulting from the bloom of a dinoflagellate and is one of a group of twelve identified compounds which vary in the distribution of H, OH and OSO_3H groups[12,16].

The last class of marine guanidines covered in this summary are the bioluminescent compounds, the luciferins. Because of their instability, the structure of only one luciferin (52), isolated from a crustacean, has been established.



(52)

4. CRITERIA FOR A CHEMICAL SYNTHESIS

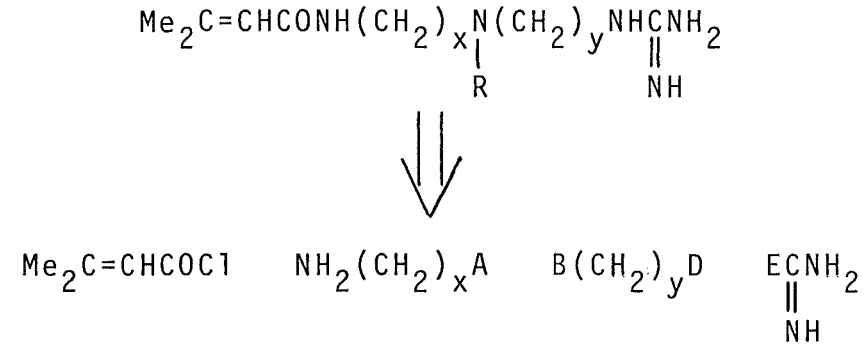
A basic premise associated with the identification of new biologically active compounds is that slight changes in the molecular structure may cause changes in the compound's biological activity. Often the activity may be diminished but many of the drugs marketed today are analogues of natural products whose activity has been increased by structural modification. As most marine guanidine compounds are biologically active, an interest in synthesizing them and their analogues exists.

The acarnidines (1), with an established biological activity, lend themselves readily to synthesis because of their relatively simple structures. The unusual unsaturation of the fatty acid chain notwithstanding, the class possesses neither rings nor chiral centres that might complicate the synthesis of analogues. The structural modification need not be a change in the functional groups but need only be a minor change in lipophilicity, as this effect can alter the ease of transport of the chemical in physiological systems. Again, the acarnidines (1) lend themselves to the synthesis of analogues by merely changing the fatty acid chain lengths. Accordingly, the synthesis of analogues of the acarnidines (1) was undertaken to determine any changes in biological activity as a consequence of structural modifications.

The preferred synthesis of the acarnidines should

be one that can be adapted to a range of synthons so that analogous compounds can be readily prepared. Ideally, the synthesis should be of the converging type which allows complex structures to be prepared from diverse but simply prepared precursors involving a minimum number of steps. Furthermore, chromatographic separations should be minimized as they are undesirable on a large scale; likewise, reactions should be adaptable to large scale preparations from cheap starting materials.

With the above points in mind, a retrosynthetic analysis was undertaken to reduce the molecule to synthetically useful starting points.



R = acyl

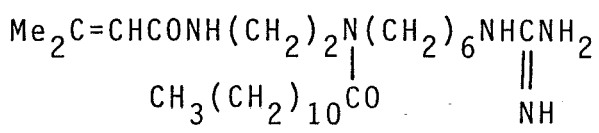
The functional groups A,B,D and E could be amines or any groups susceptible to nucleophilic substitution, while the values of x,y and R provide the choice for the acarnidine analogues. By retroanalysis, the acarnidines appeared to be susceptible to traditional synthetic methods based on judicious alkylation and acylation of amino groups. Many proposed schemes were compiled and attempted.

The homospermidine skeleton of the acarnidines

[3-aminopropyl-1,5-diaminopentane abbreviated to 3,5-homospermidine for the 3,5-acarnidines (1a-c)] also requires some consideration as spermidine alkaloids have generated a great deal of interest in recent years[17].

A suitable starting point in the total synthesis could be any α,ω-diaminoalkane or two other synthons that would combine in such a way to make the homospermidine. The reactivity of the functional groups also had to be considered, in particular, transacylation caused by intra- or intermolecular attack by a nitrogen nucleophile upon a carbonyl carbon could occur. A possibility existed that the guanidino function could also be susceptible to transacylation reactions[18]. The incorporation of the guanidino group, because of its polarity, was considered to be the key step of the synthesis.

The initial target molecule of this thesis was the analogous 2,6-acarnidine lauramide (53) as Rinehart and Gottschalk were attempting to synthesize the natural acarnidine (1a)[8].



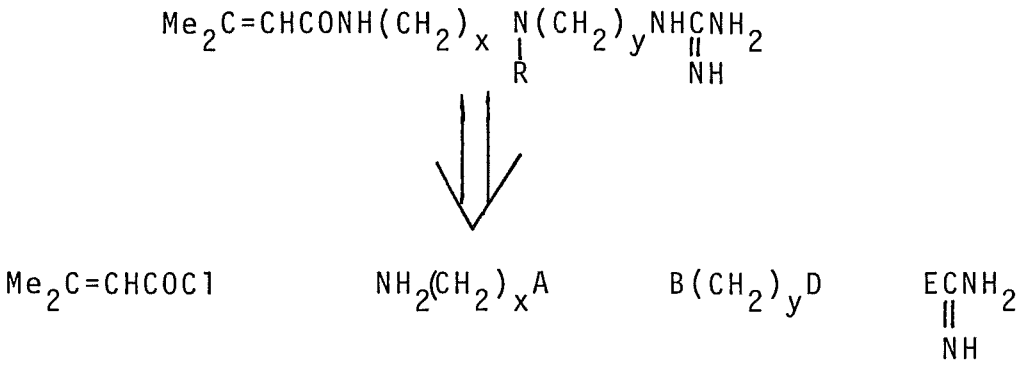
(53)

CHAPTER II

DISCUSSION AND RESULTS

1. SYNTHETIC APPROACHES TO THE ACARNIDINES

A number of points arose from the retrosynthetic analysis (see p. 22) that required further consideration.



R = acyl

The starting synthons, $NH_2(CH_2)_xA$ and $B(CH_2)_yD$, by necessity each possess one or two amino groups (or masked amino groups) which need to be selectively alkylated or acylated (See Schemes III - XIII).

Procedures for the direct alkylation of primary and secondary amines with alkyl halides or aldehydes often afford mixtures which include the tertiary amine, therefore attempts to selectively alkylate α,ω-diamines (e.g. for A or B and $D=NH_2$ or NHR) can produce not only the α,ω-dialkyl byproduct but also the tertiary amine product as well.

$$H_2N(CH_2)_yNH_2 \xrightarrow{RX} RNH(CH_2)_yNH_2 + RNH(CH_2)_yNHR + RRN(CH_2)_yNH_2$$

Protective groups exist that can reduce the nucleophilicity of diaminoalkanes by N,N'-bis-acylation followed by selective alkylation at a nitrogen.

$$RNH_2 \xrightarrow{P^*} RNHP \xrightarrow{-H^+} \overset{\ominus}{R}NP \xrightarrow{R'X} RR'NP \xrightarrow{-P} RR'NH$$

* P is an N-protective group.

Such groups include the acid labile trifluoromethanesulphonyl,[19] trifluoroacetyl[20] and phosphoryl[21,22] functions. The proposed synthesis by bis-protection is described in Scheme III. The suitability of this scheme could be realized by studying model reactions. This approach to the alkylation of amines is not an often quoted method and acylation of a phosphinamide has not been reported. As diphenylphosphinyl chloride (54) was immediately available model reactions based on this approach were investigated.

$$(C_6H_5)_2\overset{\overset{O}{\|}}{P}Cl$$

(54)

An alternative to bis-acylation of the synthons $H_2N(CH_2)_xA$ and $B(CH_2)_yD$ (A,B and D=NH_2) is the avoidance of any protection when low priced starting materials are used. For instance, a traditional method for the synthesis of spermidine (27) is by alkylation of 1,4-diaminobutane with acrylonitrile (55).

$$H_2N(CH_2)_4NH_2 + H_2C{=}CHC{\equiv}N \longrightarrow H_2N(CH_2)_4NH(CH_2)_2C{\equiv}N$$

(55)

ω-Chloroalkylnitriles can be substituted for acrylonitrile (55) for the preparation of analogues of spermidine (27). Clearly bis-alkylation can and does occur, but the products can be separated. The nitrile group is a masked amino functionality where the amino group can readily be revealed by catalytic reduction.

$$H_2N(CH_2)_4NH(CH_2)_2C{\equiv}N \xrightarrow{[H]} H_2N(CH_2)_4NH(CH_2)_3NH_2$$

(27)

This approach lends itself to the synthesis described in Schemes V and IX; however these schemes may be limited by alkylation or interference by the guanidino group or by equal acylation and guanidination of the primary and secondary amines. Nevertheless, the ease of alkylation favoured an investigation of this route.

Selective acylation of an amine in $H_2N(CH_2)_xA$ or $B(CH_2)_yD$ as described in Schemes IV, VI, VII, XII and XIII also presents problems. Traditionally acylation of diamines to form monoamides has been achieved only at great length with careful pH control on relatively few synthons.[18,23,24] The normal product of monoacylation was the N,N'-bis(amide) recovered in high yield, no matter what proportion of reagents was used. No entirely satisfactory reason for this effect has yet been proven. Recently, however, monoprotection of diaminoalkanes has

been accomplished with the aid of polymer supports[25] and activated esters of lesser reactivity than acyl halides[26]. Thus, this approach warranted attention with respect to acylation by dimethylacryloyl chloride (56) [Schemes IV, VI and VII (in VI and VII A=OH)] and by various protective groups (Scheme XII).

$$RCOCl + H_2N(CH_2)_xA \longrightarrow RCONH(CH_2)_xA$$

Protective groups themselves possess a wide range of stabilities and reactivities. They can be alkyl, acyl (and formyl), phosphoryl and sulphonyl types and depending on the group of choice may be selectively cleaved by acid or base hydrolysis, by oxidation or reduction, or by electrochemical methods, to name a few[27]. For example, the compounds described above for the partial (bis) protection of amines can be used for total protection if strong bases are avoided.

The largest class of protective groups is undoubtedly of the alkoxycarbonyl type.

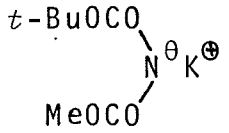
$$\underset{\underset{O}{\|}}{ROCX} + R'NH_2 \longrightarrow \underset{\underset{O}{\|}}{R'NHCOR}$$

Within the class, they possess a wide range of stabilities which can allow selective deblocking of the amine under a variety of conditions. Another advantage of the carbamates is that hydrolysis often yields gaseous or volatile byproducts. The formate protective group can be converted to the carbamate from either the chloroformate

or from a (mixed) carbonate.

Still other methods exist for the synthesis of acarnidines from the $H_2N(CH_2)_xA$ and $B(CH_2)_yD$ synthons. A method where B is a phthalimido group and D is a bromine atom in the manner of the Gabriel synthesis was devised (Scheme VIII)[28]. A recognized weakness of Scheme VIII was the possibility of nucleophilic attack by an amine upon the imide carbonyl carbon atoms; however, the advantages were the potentially rapid synthesis, with the phthalimido group being a group that is simple to handle (in terms of polarity and crystallization) and the unusual properties imparted to the primary amine by the guanidino group (*vide infra*).

Another milder method of amination and protection by the means of a "modified" Gabriel reagent, namely potassium *tert*-butyl methyl iminocarboxylate (57), has been reported[29].

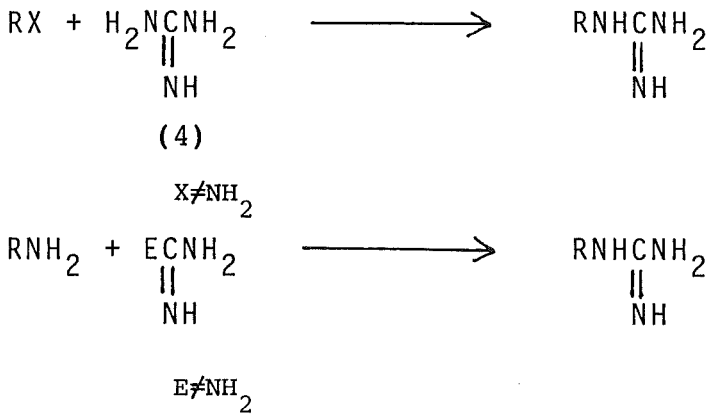


(57)

The iminocarboxylate (57) might possess the same intrinsic problem as the phthalimido group although carbamate carbonyls are less reactive to amines than imide carbonyls.

The last major consideration deriving from the retrosynthesis exercise was the formation of the guanidino function. Should it be added at the beginning or end of

the total synthesis? Should the alkylated guanidine be formed in a substitution reaction (SN_2) with guanidine (14) as the free base and an appropriate leaving group; or, by reaction of an amidinating agent (e.g. an isothiourea) with a primary amine?



The high polarity intrinsic to the guanidino group could adversely effect the synthesis if added early in the scheme (see Schemes V - XI) but conditions for guanidination at the end of the scheme (see Schemes III, IV, XII and XIII) may be difficult because of the relatively low polarity of the other synthon (see Scheme II).

In Scheme III, an alcohol group was to be converted to a better leaving group (e.g. by sulphonation[30]) so that substitution with the guanidine nucleophile can readily occur.

Alternatively, the alcohol could be converted to an amine[8,31] which could be amidinated. An advantage of amidination of an amine [B or D in $B(CH_2)_yD$][32,33] early in the sequence (Schemes V - XI) as compared to the last step, allows for a wide scope in the choice of synthons and

furthermore the intermediate guanidino compounds could be tested for biological activity.

The effect of the guanidino group upon reactions subsequent to its incorporation was not clear, although the question has arisen in peptide syntheses.

Much of the stimulus for research into protection of the guanidino group has been created by the need to synthesize peptides. Although arginine (7) is one of the essential amino acids, synthesis of peptides including this amino acid are less common because of the problems associated with the guanidino group. As previously implied protonation of guanidine is a form of protection, but protonation inhibits solubility and reactivity. Many protection methods often do not completely block the guanidine group allowing side reactions to occur [e.g. *p*-toluenesulphonyl (tosyl), nitro, *tert*-butyloxycarbonyl] while other methods successfully block the group but only in moderate yields (e.g. benzyloxycarbonyl)[34]. Often when the guanidine group has been protected, deprotection is difficult because of the forcing conditions required (e.g. tosyl and nitro) or because of steric or rearrangement problems (e.g. isobornyloxycarbonyl, adamantyloxycarbonyl)[35-39]. Nevertheless, arginine (7) can be successfully protected and the difficulties often relate to unique cases. A base labile protective group has been developed[40] and also another group labile in trifluoroacetic acid has also recently been announced[41].

Another aspect of guanidination is that primary amines have been reported to be more reactive to

amidination compared to secondary amines when the reaction is undertaken at room temperature (see Scheme IX)[33]. This feature, although not universal[10], can be explained in terms of the mechanism[42]. In an aqueous solution heated at reflux, isothiouronium salts can be thermally degraded to cyanamide (5). In a solution heated in the presence of an amine the salt may form an intermediate composed of either the thiouronium ion, or its conjugate base or possibly cyanamide (5) itself.

$$RNH_2 + \left[\begin{matrix} H_2N-C-NH_2 \\ | \\ SR \end{matrix}\right]^+ \rightleftharpoons RNH_3^+ + \begin{matrix} H_2N-C=NH \\ | \\ SR \end{matrix} \rightleftharpoons RSH + \underset{(5)}{H_2NC\equiv N}$$

Since the pKa of the isothiourea is 9.9 the conjugate base would be 75% of the initial equilibrium.

The strongly electrophilic thiouronium ion affords an intermediate with amines of lower activation energy favouring the desired reaction pathway rather than formation of the conjugate base. The formation of cyanamide (5) is accordingly less likely at room temperature where reaction would occur via the thiouronium ion or its conjugate base.

Every scheme devised for the synthesis of the acarnidines (1) possessed strengths and weaknesses. Some of the weaknesses can be readily acknowledged but they could be outweighed by a synthesis of a few steps (e.g. Scheme IV) or by gaining average yields from low cost synthons (e.g. Scheme IX).

Guanidination (protected or unprotected) at an early stage of the synthesis appeared to be a favourable

approach because of the potential biological activity of the intermediate compounds. Selective protection of an α,ω-diaminoalkane was less favoured initially. Some schemes that were less certain of success were attempted because the reagents were immediately available.

2. ATTEMPTED PREPARATIONS OF THE ACARNIDINES

This section describes in detail a number of synthetic approaches to the acarnidines that were devised and undertaken experimentally. None of these schemes were satisfactory and were abandoned in favour of the successful synthesis that is described in Section 3 of the Discussion.

Although Section 2 describes the failures, the information gained from some of the syntheses suggested that several routes to the acarnidines could succeed. The synthesis in Section 3 realized some early successes that necessitated the cessation of further investigation of other methods.

2.1 From 1,2-Diaminoethane

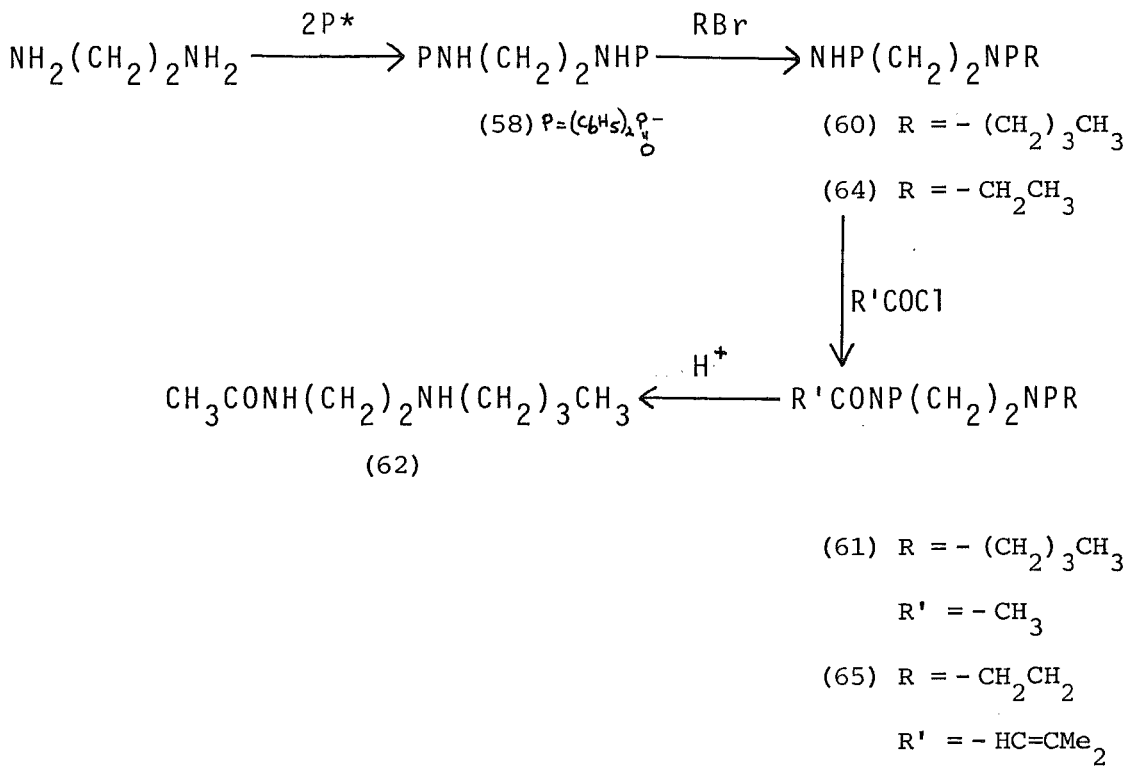
1,2-Diaminoethane is the retrosynthetic synthon $H_2N(CH_2)_xA$ in which x = 2 and A = NH_2.

2.1.1 *Via* Bis-Protection

Scheme III describes the proposed route to the

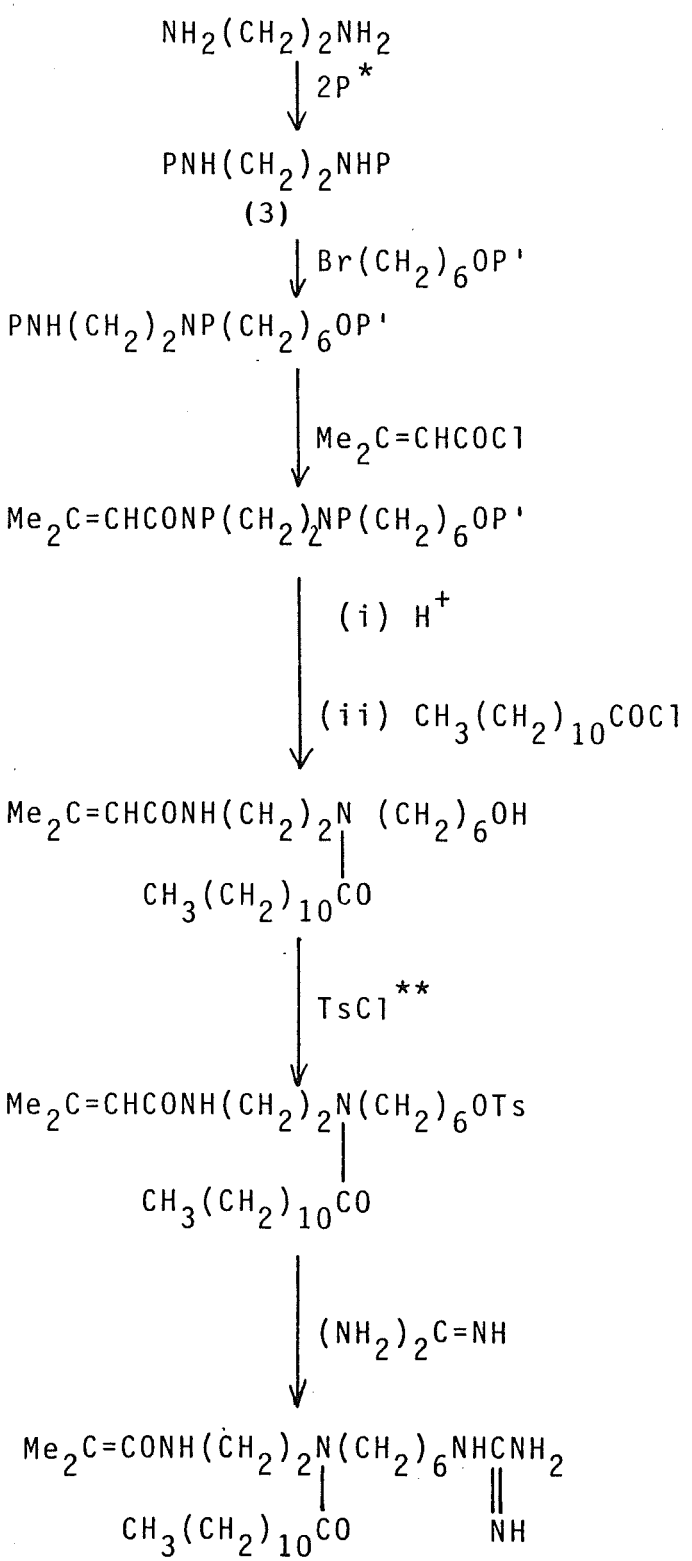
2,6-acarnidine (53) *via* bis-protection.

Initially, to ensure that the diphenylphosphinamide (58) could satisfy the criteria, a series of model reactions were undertaken.



* P is an amine protective group [$(C_6H_5)_2P(=O)$ —]

Diphenyphosphinyl chloride (54), prepared by bubbling oxygen through chlorodiphenylphosphine (59)[43], was reacted with diaminoethane to form ethylenebis(diphenyl-phosphinamide) (58)[44]. The phosphinamide (58) was butylated at only one nitrogen atom in tetrahydrofuran using sodium hydride as the base[21]. The reaction was monitored by thin layer chromatography (t.l.c.) (as were most of the reactions) and the N-butyl phosphinamide (60) was isolated as an amorphous solid when no more starting material was observed. After unsuccessful attempts to



* P and P' are protective groups

** Ts is the p-toluenesulphonyl group

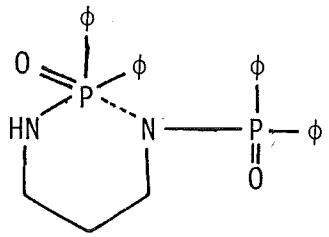
SCHEME III

crystallize the butyl phosphinamide (60), its structure was confirmed by nuclear magnetic resonance (n.m.r.) spectroscopy and the purity was determined by t.l.c. Acylation of the other nitrogen atom of the phosphinamide (60) with acetyl chloride was achieved using sodium hydride as the base to yield the phosphinamidoamide (61) as an oil in reasonable yield and purity. Mass spectrometry did not measure a parent ion, but meaningful daughter ions were detected. Deprotection of the phosphinamidoamide (61) to the amide (62) was readily achieved by hydrolysis using Ramage's method of hydrochloric acid in a 2:1 mixture of dioxan/water[21]. The amide (62) was extracted from the acidic work up fraction (after the dioxan was removed) using 2-butanol, as it is a very polar extraction solvent.

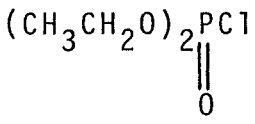
As the mechanics of the scheme seemed to be straightforward, more exploratory reactions related to Scheme III were attempted. The phosphinamide (58) was to be alkylated with methyl iodide to simplify analysis, followed by acylation with 3,3-dimethylacryloyl chloride (56), deprotection of the nitrogen atoms and subsequent acylation. Attempts to methylate the phosphinamide (58) failed. In addition to the above method, hexamethylphosphoramide (HMPA) was added to the tetrahydrofuran to utilize its catalytic effect. A two phase reaction was also attempted.

Ethylation of the phosphinamide (58) succeeded by the standard method to produce the N-ethyl product (64) whose purity was checked by high performance liquid chromatography (h.p.l.c.). Accordingly, 3,3-dimethyl-

acryloyl chloride (56) was prepared but acylation of the phosphinamide (58) to the amide (65) was unsuccessful. Only the unreacted phosphinamide (58) was recovered. Steric hindrance around the nitrene (N:) could have prevented the approach of the acyl chloride (56). The nitrene might also have been stabilized by the ε-phosphorus atom.



An alternative to diphenylphosphinyl chloride (54) would be diethyl chlorophosphate (66)[4], which would reduce the steric interactions. However, apart from the other described problem, Zwierzak[2] stated that diethyl phosphoramidates are less readily alkylated than the diphenylphosphinamides.



(66)

As a result of the complications encountered, this approach was not pursued.

2.1.2 Guanidination *via* Nucleophilic Substitution on Carbon

Another major factor that needed to be clarified in Scheme III was the conversion of the alcohol to a

guanidine.

The mildest method under which the appropriate guanidination would occur was that of Munro[30]. The alcohol was to be sulphonated with *p*-toluenesulphonyl chloride and the sulphonate displaced by free guanidine (4).

Octanol was chosen as the model alcohol because its lipophilicity was akin to the acarnidine precursor. Octanol was readily converted to the sulphonate (67).

$$CH_3(CH_2)_7OH \xrightarrow{TsCl} CH_3(CH_2)_7OTs \xrightarrow{(NH_2)_2C=NH} CH_3(CH_2)_7NHC(=NH)NH_2$$

(67) (68)

The nucleophilic substitution by guanidine (4), converted to the free base with sodium *tert*-butoxide, failed to form the N-octylguanidinium compound (68). Hydrolysis of the sulphonate (67) occurred forming guanidinium tosylate (69) which was confirmed by comparison with the tosylate (69) formed by neutralization of guanidinium carbonate with *p*-toluenesulphonic acid.

Another leaving group is the bromide ion. Gottschalk[8] unsuccessfully had attempted to convert an alcohol to the guanidine *via* the bromide (70) based on the method of Olomucki and Hebrard[45], (Scheme II).

$$Me_2C=CHCONH(CH_2)_3\,\underset{\displaystyle CO(CH_2)_{10}CH_3}{\overset{\displaystyle N(CH_2)_5Br}{|}}$$

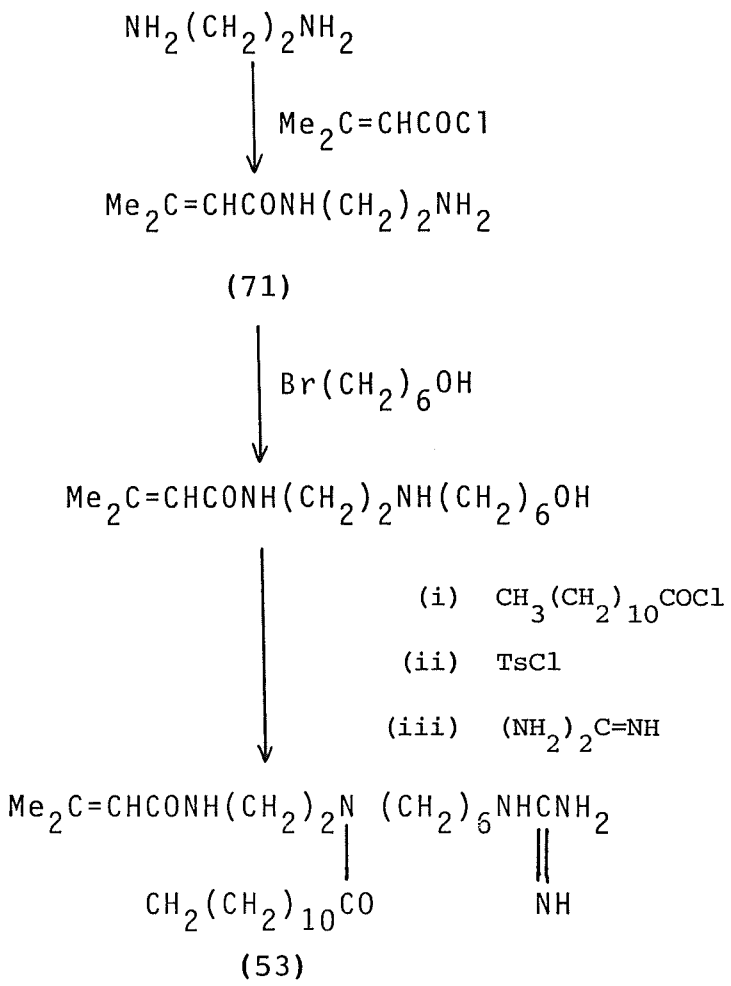
(70)

Gottschalk had also proposed a scheme similar to Scheme III but he was unable to prepare the bromo compound. A reason suspected for the failure of guanidination at the last step of Gottschalk's attempted synthesis (Scheme II) is that the hydrophobic portions of the bromide (70) [and the sulphonate (67)] wound around the reaction site in the polar reaction solvent preventing the SN_2 reaction[8]. Also, the free guanidine (4) would be heavily solvated in the protic solvents. Guanidination of small or rigid alkyl halides and sulphonates has been successful under similar conditions. Conversion of the halide (70) to an amine for subsequent guanidination with an S-alkylisothiourea was also unsuccessful[8].

The failure to prepare an alkylguanidine from a tosylate or from a bromide coupled with the inability to prepare the acrylamide (65) enforced the adoption of a new approach.

2.1.3 Without Bis-Protection.

If N-(2-aminoethyl)-3,3-dimethylacrylamide (71) could be prepared even as a small proportion from the low priced starting materials, a rapid synthesis of the 2,6-acarnidine (53), according to Scheme IV, would be achieved.



SCHEME IV

3,3-Dimethylacryloyl chloride (56) was added to 1 mole equivalent of diaminoethane with triethylamine as the added base. Only the 1,2-bis(acyl)diaminoethane (72) in quantitative yield was isolated.

$$Me_2C{=}CHCONH(CH_2)_2NHCOCH{=}CMe_2$$

(72)

The reaction was repeated without added base so that unreacted amino groups would trap the hydrogen chloride with the possibility that one of the amino groups per molecule would react with the acyl chloride (9). The required product,

N-(3-aminioethyl)-3,3-dimethylacrylamide chloride (71.HCl) was recovered by filtration in a quantitative yield.

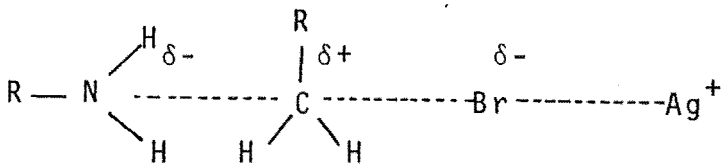
The next reaction in Scheme IV was the alkylation of the primary amine (71). A model reaction was investigated.

$$Me_2C{=}CHCONH(CH_2)_2NH_2 + CH_3(CH_2)_3Br \longrightarrow Me_2C{=}CHCONH(CH_2)_2NH(CH_2)_3CH_3$$

(71) (73)

The reaction was to be a nucleophilic substitution using bromobutane and one mole equivalent of base, however only 1,2-bis(acyl) product (72) was isolated. When the free amine was formed, intermolecular transacylation was the preferred reaction.

The alkylation was attempted in organic, two phase and aqueous solutions with a variety of bases. Silver nitrate was also used as it could be precipitated with the chloride ion to free the amine and also be used to facilitate the removal of the bromide activating the SN_2 reaction. By no method available could the transacylation be prevented. This method was therefore unsuitable.



2.2 From N-(6-Aminohexyl)guanidine

As guanidination at the last step of the acarnidine synthesis failed (Schemes II, III and IV) it was appropriate to incorporate the guanidino function in an earlier reaction

of the total synthesis. Possible syntheses from N-(6-aminohexyl)guanidine (74) are shown in Schemes V - VII.

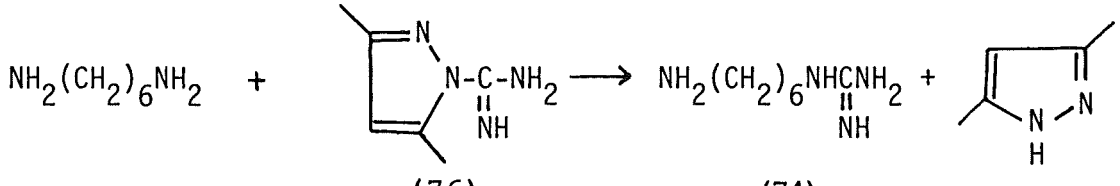
2.2.1 Preparation of N-(6-Aminohexyl)guanidine.

There are several methods available for the guanidination of amines[32,33], but results of monoguanidination of α,ω-diaminoalkanes is concealed in patents[46]. Monoguanidination of 1,5-diaminopentane by Carter was achieved only in very low yield[8]. Nevertheless, as the series of ω-aminoalkylguanidines up to N-(5-aminopentyl)guanidine had been prepared from α,ω—diaminoalkanes the synthesis of N-(6-aminohexyl)guanidine (74) was investigated. 1,6-Diaminohexane was chosen because of its immediate availability and low cost. Two general routes looked promising. The first attempts were in aqueous solution and in ethanolic solution using the diamine with S-methylisothiouronium sulphate (75).

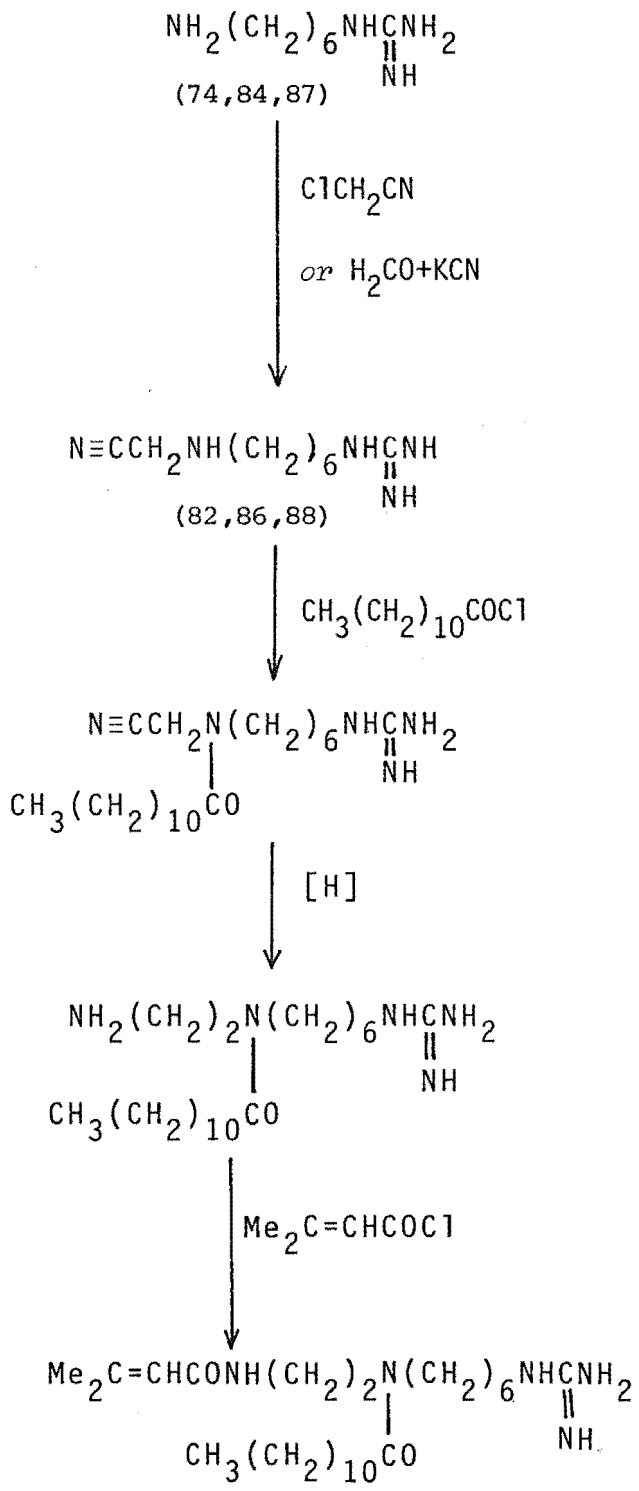
$$NH_2(CH_2)_6NH_2 + CH_3SC(=NH)NH_2 \longrightarrow NH_2(CH_2)_6NHC(=NH)NH_2 + CH_3SH$$

(75) (74)

The second scheme was by reaction of the diamine with 1-guanyl-3,5-dimethylpyrazolium sulphate (76) in ethanol or without solvent in a fusion mixture[32].

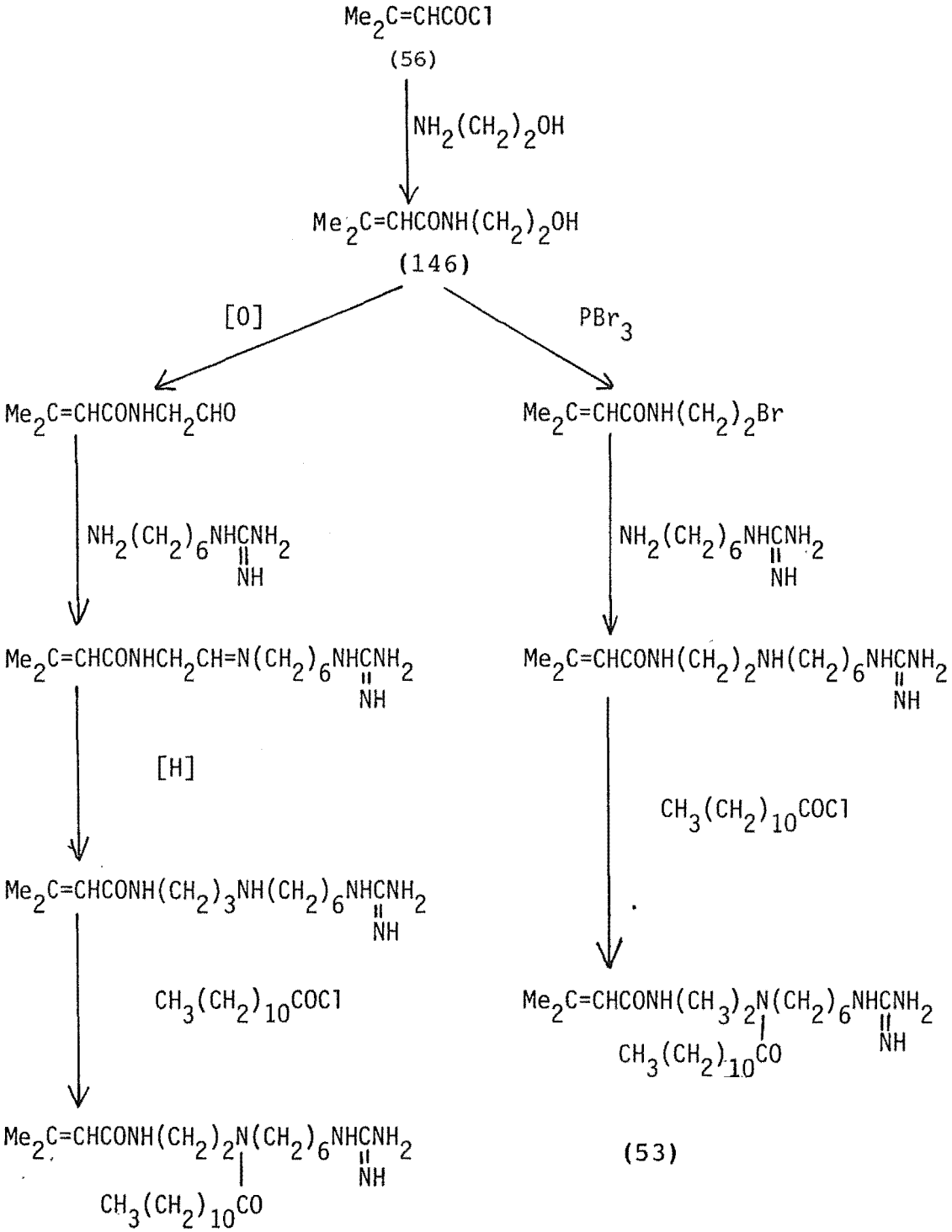


(76) (74)


NH2(CH2)6NHCNH2
NH
(74,84,87)
ClCH2CN
or H2CO+KCN
N≡CCH2NH(CH2)6NHCNH
NH
(82,86,88)
CH3(CH2)10COCl
N≡CCH2N(CH2)6NHCNH2
NH
CH3(CH2)10CO
[H]
NH2(CH2)2N(CH2)6NHCNH2
NH
CH3(CH2)10CO
Me2C=CHCOCl
Me2C=CHCONH(CH2)2N(CH2)6NHCNH2
NH
CH3(CH2)10CO

(53)

SCHEME V



SCHEME VI

SCHEME VII

S-Methylisothiouronium sulphate (75) was prepared from thiourea and dimethylsulphate, and pyrazole (76) was prepared from aminoguanidine (77) and 2,4-pentanedione.

In the ethanol solution after a 2 h reflux the pyrazole method afforded N-(6-aminohexyl)guanidine (74) in 10% yield compared to the 76% yield of 1,6-bis(guanidino)-hexane (78). The two compounds were separated by selective crystallization from acetone/water. After the pyrazole-amine fusion mixture had been heated at 80° for 2 h a quantitative recovery of the 1,6-bis(guanidine) (78) was recovered.

Similarly, when S-methylisothiouronium sulphate (75) was used in aqueous solution only a 20% crude yield of aminohexylguanidine (74) was recovered. In ethanol solution, however, a 50% yield of purified aminohexylguanidine (74) was isolated. The products were unambiguously identified by ^{13}C n.m.r. as the symmetrical 1,6-bis(guanidine) (78) which possessed 4 peaks compared to the 7 peaks indicative of N-(6-aminohexyl)guanidine (74). The distinction in the melting points and infrared spectra became apparent only after each compound was identified.

2.2.2 From Chloroacetonitrile.

Chloroacetonitrile (79) has been reported to be a convenient reagent for direct cyanomethylation of amines without the formation of N,N-bis(cyanomethyl) derivatives[47]. As the primary amine is a stronger nucleophile than the guanidino function, there appeared to be no need for a

guanidine protective group beyond protonation in the scheme (Scheme V). Chloroacetonitrile (79) was prepared in two steps. A cold solution of chloroacetyl chloride in benzene was converted to α-chloroacetamide (80) with dry gaseous ammonia. The nitrile (79) was formed by distillation off phosphorus pentoxide in 30% overall yield.

$$ClCH_2COCl \xrightarrow{NH_3} \underset{(80)}{ClCH_2CONH_2} \xrightarrow{P_2O_5} \underset{(79)}{ClCH_2C{\equiv}N}$$

A model reaction of chloroacetonitrile (79) with 2-aminioethylbenzene chloride (81) was successfully achieved in three solvents: benzene, pyridine and ethanol, all of which afforded 2-(cyanomethylamino)-ethylbenzene (82) in about 55% yield with no evidence for the N,N-bis(cyanomethyl) product.

$$\underset{(81)}{C_6H_5(CH_2)_2NH_2} \xrightarrow{ClCH_2CN} \underset{(82)}{C_6H_5(CH_2)_2NHCH_2C{\equiv}N}$$

N-(6-Aminohexyl)guanidine (74) is insoluble in most organic solvents including methanol and pyridine so the first attempt at the cyanomethylation of the amine (74) to form the secondary amine (83), as described in Scheme V, was undertaken in aqueous solution, but without success. The reaction was repeated in water but with one mole equivalent of sodium bicarbonate added. As the amine (74) was soluble in dimethylformamide, the

reaction was also attempted in that solvent but none of the attempts were successful.

As the cyanomethylation of 2-aminoethylbenzene (81) was successful in less polar solvents, the guanidinium sulphate (74) was converted to the organic solvent soluble salt, the tetraphenylborate (84). The tetraphenylborate anion is an ion well known for its ability as a counter-ion for dissolving metal cations in organic solvents. As the sodium salt (85) is very expensive a quantity was synthesized from the Grignard reagent, phenylmagnesium bromide, and sodium tetrafluoroborate in tetrahydrofuran[48]. N-(6-Aminohexyl)guanidinium tetraphenylborate (84) was prepared simply by mixing aqueous solutions of sodium tetraphenylborate (85) and the guanidinium sulphate (74). The guanidinium tetraphenylborate (84) was isolated by filtration and identified by n.m.r.

Cyanomethylation of the amine (84) to form the secondary amine (86) was attempted in tetrahydrofuran, acetonitrile and pyridine without success at room temperature or at reflux temperature.

N-(6-Aminohexyl)guanidinium iodide (87) was subsequently prepared [when reaction of the borate (84) was unsuccessful] to ensure that the large anion had not prevented the alkylation reaction from occurring. The iodide (87) was prepared from the sulphate (74) by ion exchange chromatography on Amberlite IRA 400 (I^-) resin. The location and purity of the exchanged compound was monitored by Sakaguchi reagent (which specifically

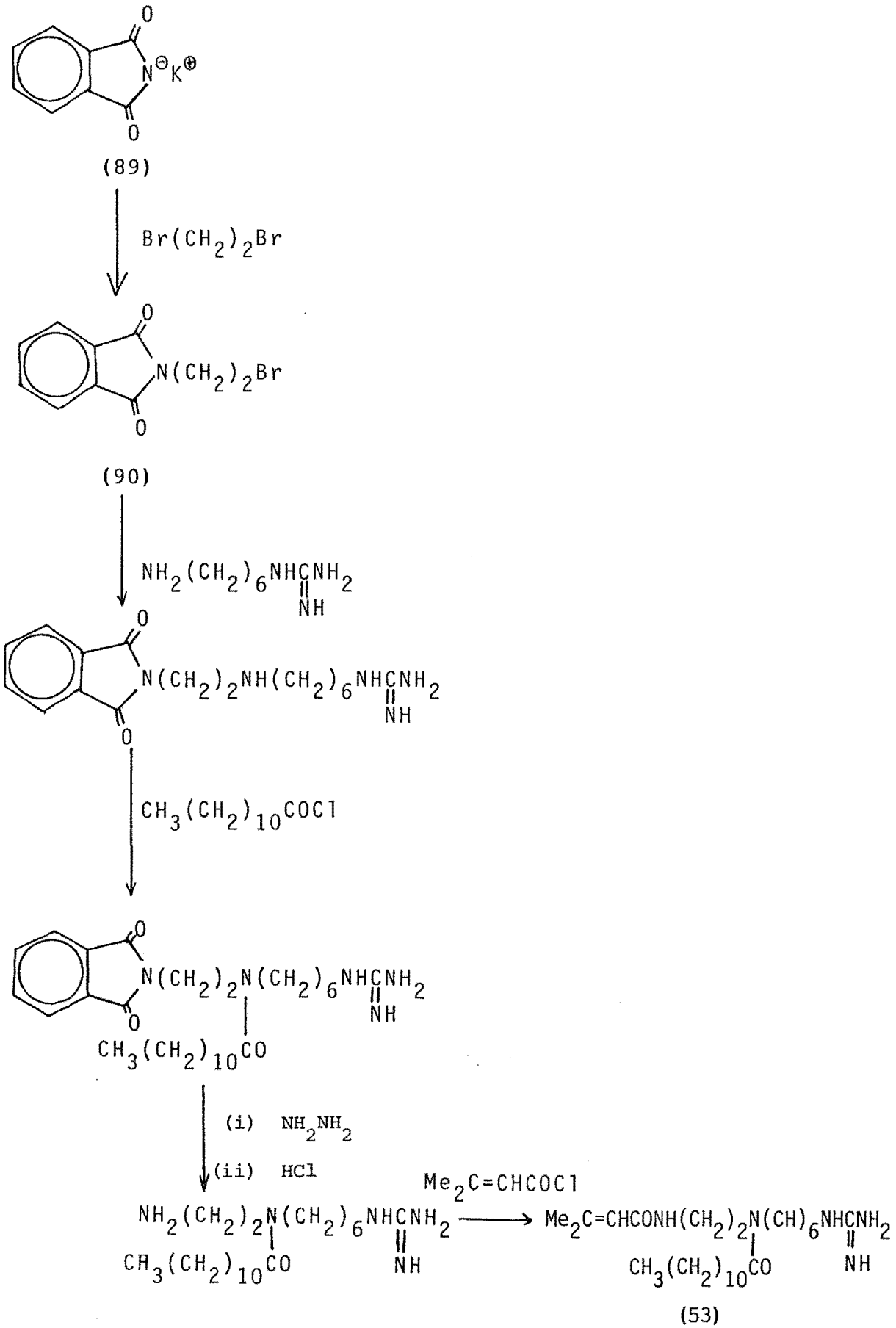
identifies monosubstituted guanidines; by formation of a red colour), silver nitrate (for iodide) and barium chloride (for sulphate) spot tests on the column eluate. The ultraviolet spectrum of the guanidinium iodide (87) was also recorded showing a maximum absorption at 217 nm (ε 16 000). The sulphate (74) showed only weak end absorption at <200 nm. The differences in the ultraviolet spectra were characteristic of the anions as the guanidinium cation is not a chromophore[18,49].

The reaction of chloroacetonitrile (79) and the iodide (87) in methanol to form the secondary amine (88) however, was unsuccessful. No reaction was evident.

In conclusion, direct alkylation of N-(6-aminohexyl)guanidine (74,84,87) with chloroacetonitrile (79) (Scheme V) did not yield the secondary amine under a variety of conditions. (For the modified Strecker synthesis refer to Section 2.3.6.1).

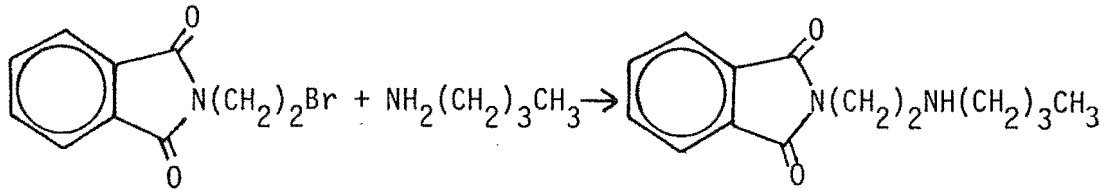
2.2.3 From N-(2-Bromoethyl)phthalimide

The proposed synthetic method from potassium phthalimide (89) is pictured in Scheme VIII. N-(2-bromoethyl)phthalimide (90) was prepared by heating a fusion mixture of potassium phthalimide (89) and 1,2-dibromoethane[50]. The isolated alkylphthalimide (90) was then heated at reflux in ethanol with aminobutane in a model reaction.



(53)

SCHEME VIII



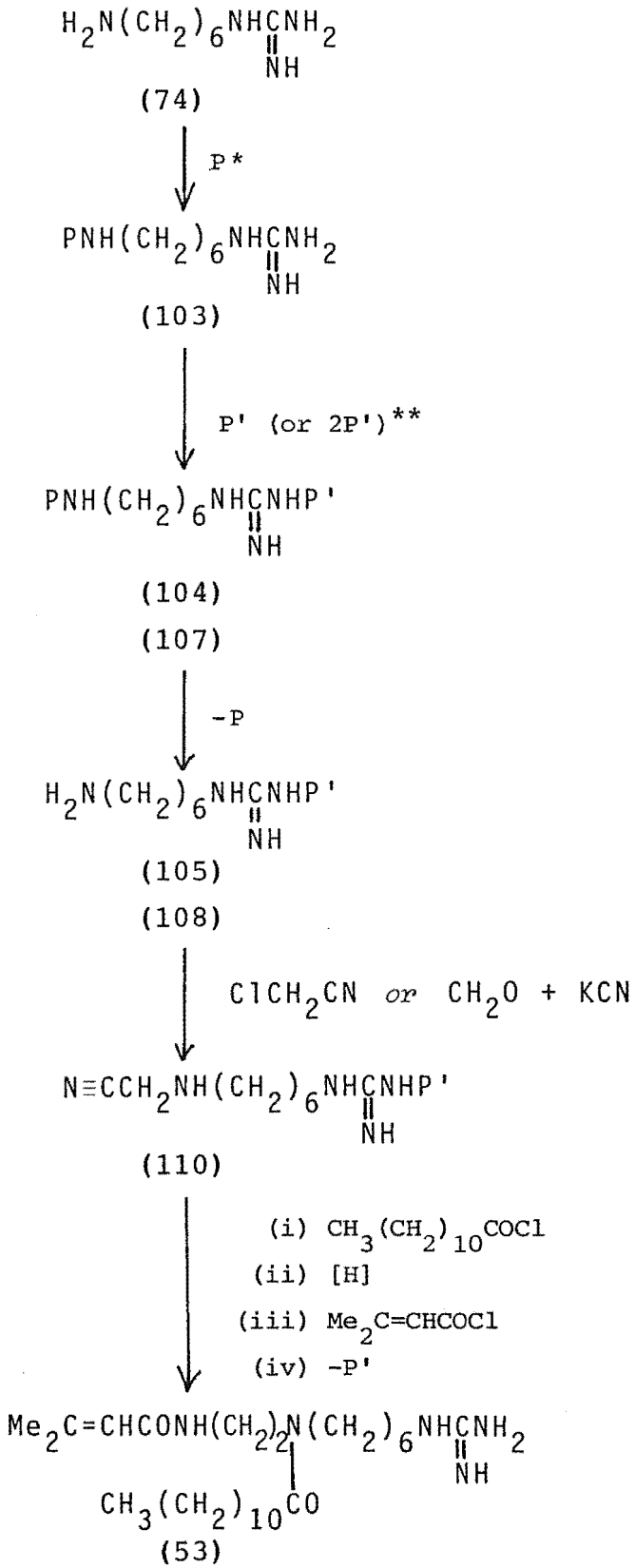
(90) (91)

A mixture whose components were not identified was recovered, also N-(butylaminoethyl)phthalimide (91) was not observed by n.m.r. Kormendy *et al.*[51] have reported that reactions similar to the one attempted cause cleavage of the phthalimide ring to form unidentified oxazolines or phthalamidines.

As the organic solvent soluble guanidine salts (84, 87) influence the primary amine, an attempt to prepare the secondary amine (92) was undertaken by heating at reflux in ethanol N-(6-aminohexyl)guanidine (84) and 2-bromoethylphthalimide (90). The result was the same as that in Section 2.2.2: no reaction was observed, thus another synthetic method was investigated.

2.3 From Guanidine Protected N-(6-Aminohexyl)-guanidine.

The failure to prepare an acarnidine, after incorporation of the protonated guanidino group early in the synthesis (Schemes V and VII[8]), did not detract from the advantages of the preparation of precursors containing the guanidino group in some form. As described in Section 1 of the Discussion, the guanidine function of N-(6-aminohexyl)guanidine (74) could be protected by the same methods available for the protection of arginine (7) as elaborated in Scheme IX. Three protective groups were



SCHEME IX

*P = $C_6H_5CH_2OCO$ –

**P' - Tosyl or 2(isobornyloxycarbonyl)– bonded to two nitrogen atoms.

prepared to increase the variety of derivatives suitable for selectively blocking the primary amine and the guanidine.

2.3.1 Preparation of Formate Protective Groups

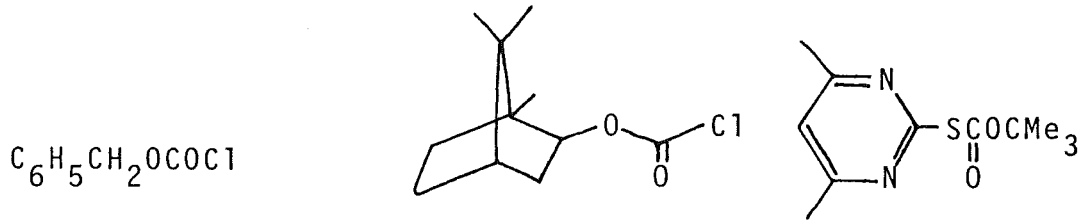
Three protective groups were synthesized from phosgene (93). The phosgene (93) was prepared by dripping carbon tetrachloride on to 100% sulphuric acid at 125° [52].

$$3CCl_4 + 2H_2SO_4 \xrightarrow{\Delta} 3COCl_2 + 4HCl + S_2O_5Cl_2$$

(93)

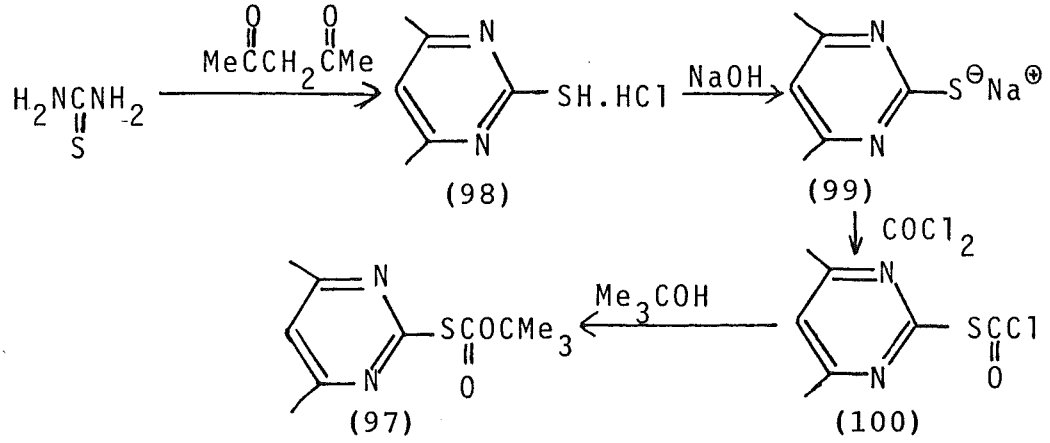
Benzyl chloroformate (94) was prepared from benzyl alcohol and phosgene (93), dissolved in toluene[53].

Isoborneol (95) (prepared by base hydrolysis of isobornyl acetate) was dissolved in ether and treated with phosgene (93) to form isobornyl chloroformate (96). Isobornyl chloroformate (96) was prepared according to the method of Fujino *et al.*[39] who did not use added base to neutralize the hydrogen chloride that was generated (compare with the method of Jäger and Geiger[38]). Although Fujino stated that isobornyl chloroformate (96) was stable, the compound was found to be unstable, possibly because the hydrogen chloride promoted acid-catalysed hydrolysis, elimination and rearrangement reactions, as shown by ^{13}C n.m.r. spectroscopy.



(94) (96) (97)

The third protective group was an acid labile mixed carbonate (97) which has been successfully used to monoprotect 1,6-diaminohexane[26] (*vide infra*). The thiocarbonate (97) was prepared by a series of reactions from thiourea and 2,4-pentanedione. The two compounds cyclized in a solution of ethanol and hydrochloric acid to form 4,6-dimethyl-2-thiopyrimidinium chloride (98). The chloride (98) was converted to the sodium salt (99) by the mixing of the chloride into a concentrated aqueous solution of two mole equivalents of sodium hydroxide followed by precipitation from acetone. The sodium salt (99) was dried and ground to a powder before being suspended in pet. ether. Liquid phosgene (93) was poured into the well-stirred suspension and after filtration and evaporation the carbonyl chloride (100) was isolated. The yield of the carbonyl chloride (100) was less than that reported by Nagasawa *et al.*[54]. The reaction was undertaken six times with yields ranging from 9-65%. The method was not changed between batches. Contrary to the literature the carbonyl chloride (100) rapidly decomposed, thus it was reacted immediately with *tert*-butanol in pyridine to form *tert*-butyl 4,6-dimethyl-2-thiopyrimidinyl carbonate (97).



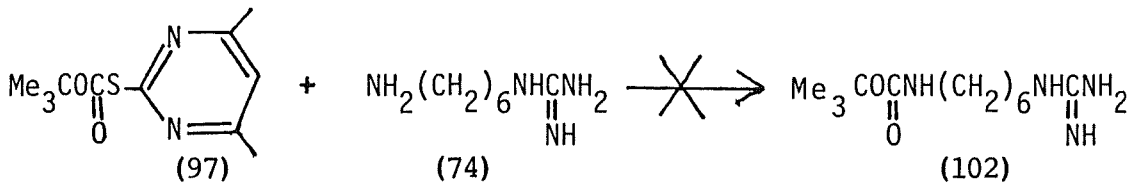
The benzyloxycarbonyl protective group is labile in mineral acid and to catalytic hydrogenolysis whereas the *tert*-butyloxycarbonyl and isobornyloxycarbonyl groups are resistant to reductive cleavage but are rapidly hydrolysed in formic or trifluoroacetic acids.

2.3.2 From the Diphenylphosphinyl Protective Group

The first attempt at Scheme IX failed. Diphenylphosphinyl chloride (54) was added to aminohexylguanidinium tetraphenylborate (84) in pyridine but the product (101) sought was not formed.

2.3.3 From the *tert*-Butyl 4,6-dimethyl-2-thiopyrimidine carbonate Protective Group

The *tert*-butyl thiocarbonate (97) was reacted with N-(6-aminohexyl)guanidine (74) in 33% aqueous dioxan. The carbamate (102) was not observed.



2.3.4 From the Benzyloxycarbonyl and Isobornyloxycarbonyl Protective Groups

When an aqueous solution of sodium bicarbonate and aminohexylguanidine (74) at 0° was treated with benzyl chloroformate (94) in a Schotten-Baumann reaction, N-[(6-benzyloxycarbonylamino)hexyl]guanidine (103) was isolated. The next reaction required deactivation of the guanidino group. The strongly acidic conditions required for nitration precluded the use of the often quoted nitro-group, thus acylation was considered to be the most suitable method.

The isobornyloxycarbonyl group can be introduced twice to the guanidino function to completely neutralize it, furthermore the groups are acid labile[38]. Two mole equivalents of isobornyl chloroformate (96) and sodium hydroxide were added in a series of small alternate portions to an aqueous solution of the guanidine (103) at 0° to afford the N,N'-bis(isobornyloxycarbonyl) compound (104). The product required purification by chromatography as there were a number of impurities associated with the protective group.

Removal of the benzyl group to form the amine (105) was attempted by hydrogenation in the presence of 5% palladium on charcoal; however, reaction was very slow and three compounds were formed. As a check on the efficacy of the acid hydrolysis of the isobornyloxycarbonyl group the protected guanidine (104) was heated at reflux in trifluoroacetic acid to afford N-[(6-benzyloxycarbonylamino)hexyl]guanidine (106).

2.3.5 From the Benzyloxycarbonyl and *p*-Toluenesulphonyl Protective Groups

As the benzyloxycarbonyl group could not be cleaved cleanly by catalytic hydrogenolysis, the protection of the guanidino group was modified so that acid hydrolysis of the benzyloxycarbonyl group could be attempted. The tosyl group is a less acid labile function than the benzyloxycarbonyl group, hence selective acid hydrolysis became viable. Traditionally the tosyl group required sodium in liquid ammonia and other powerful reagents to facilitate removal, however hydrofluoric acid/anisole[37], methanesulphonic acid and tris(trifluoracetyl)borane[35] have been cited as efficient but relatively mild deblocking reagents.

The guanidine (103) was sulphonated[36] to form N-[(6-benzyloxycarbonylamino)hexyl]-N'-(*p*-toluenesulphonyl)-guanidine (107) in 48% yield after purification as described in Scheme IX.

Initially, catalytic hydrogenolysis to form the primary amine (108) was attempted to ensure that the isobornyloxycarbonyl groups were not responsible for the poor reaction[38] previously described. The same method produced three compounds, as before.

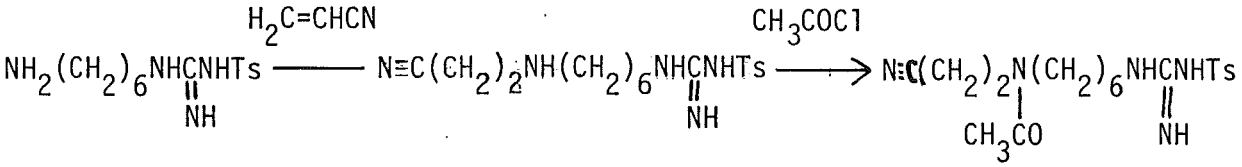
Another method of cleavage, proton transfer hydrogenation, was also attempted[56]. Proton transfer hydrogenation utilizes formic acid in the presence of palladium instead of the more elaborate requirements associated with hydrogen gas. No reaction occurred.

Acid hydrolysis proved to be a good method of deblocking the amine (107)[57]. The best yield of primary

amine (108) (88%) was achieved by dilution of commercial 40% hydrogen bromide in acetic acid to 20% hydrogen bromide with acetic acid.

As less stringent conditions were necessary to cyanoethylate the primary amine [compare the preparation of the cyanoethylamine (109) to the preparation of the cyanomethylamine (110)] trial reactions were begun with acrylonitrile (55)[58]. The primary amine (108) in methanol was treated with acrylonitrile (55) to afford N-[6-(cyanoethylamino)hexyl]-N'-*p*-toluenesulphonylguanidine (109). Some N,N-bis(cyanoethyl) compound (111) was also formed.

The secondary amine (109) was acetylated to form the amide (112) in dichloromethane as the acetyl methyl would be a readily identified n.m.r. marker.



(108) (109) (112)

2.3.6. *Via* Chloroacetonitrile

When alkylation of the primary amine (108) was attempted with chloroacetonitrile (79), as described in Schemes X and XII (*vide infra*), a low yield of the secondary amine (110) was obtained. Although a variety of solvents and conditions were used, the optimum yield was only 20% when the reaction mixture was heated to 75° with potassium carbonate in aqueous HMPA.[59]

2.3.6.1 *Via* the Modified Strecker Synthesis

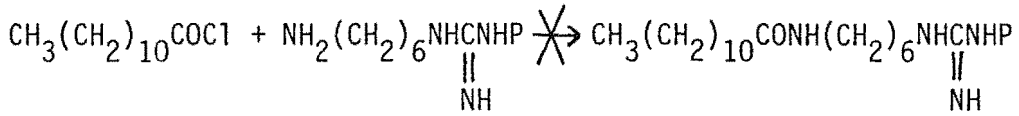
An alternative and more traditional method of cyanomethylation of amines is the Knoevenagel-Bucherer modification of the Strecker synthesis in which formaldehyde and potassium cyanide are used[60]. A method utilizing a bisulphite-formaldehyde addition complex resulted in the formation of an intractable blue gum with the primary amine (108). A second method which did not use bisulphite afforded the nitrile, after being stirred overnight at room temperature, in 43% yield.

As the modified Strecker synthesis was undertaken in aqueous solution and aminohexylguanidine (74) is water soluble, cyanomethylation of the amine (74) to form N-[6-(cyanomethylamino)hexyl]guanidine (83) was attempted (see Scheme V). Neither method afforded the secondary amine (83).

2.3.7 *Via* Acylation of the Primary Amine

As benzyl chloroformate (94) was successfully reacted with aminohexylguanidine (74), an attempt was made to acylate the amino function of aminohexylguanidine (74) by the same method. This acylation, if successful, would have provided a useful start to the synthesis of analogues based on an N-substituted amide and also to the synthesis of the polyandrocarpidines[61] (37). Dodecanoyl chloride (113) and aminohexylguanidine (74) were reacted in an attempt to form the amide (114). With sodium bicarbonate as the base in a two phase system of water

and toluene, but only a non-polar compound, negative to the Sakaguchi test, was isolated.

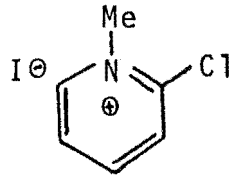


(74) P = H (114) P = H

(108) P = Ts (115) P = Ts

The failure of the Schotten-Baumann reaction led to the use of the tosyl-protected guanidine (108). Acylation of N-(6-aminohexyl)-N'-(*p*-toluenesulphonyl)guanidine (108) with dodecanoyl chloride (113) to form the amide (115) was attempted in pyridine; however, only hydrolysis of the acyl chloride occurred.[8]

An alternative method of acylation is by activation of a carboxylic acid with 1-methyl-2-chloropyridinium iodide (116) followed by reaction with an amine[62]. When this method was followed in an attempt to prepare N-[6-(*p*-toluenesulphonyl)-guanidinohexyl]dodecanamide (115) an intractable mixture of products were formed with no evidence of amidation having occurred.



(116)

2.3.8 *Via* Nitration

The nitro group, as a traditional guanidine protective group, could stabilize the guanidine yet allow reactions to occur at the primary amine of N-(6-aminohexyl)-N'-nitroguanidine (117). Treatment of a mixture of

aminohexylguanidine (74) and ammonium nitrate with concentrated sulphuric acid[63] did not yield the nitroguanidine (117) (see Discussion, Section 2.7). A possible side reaction; namely oxidation of the primary amine, could have occurred.

$$RNH_2 \xrightarrow{[O]} RNO_2$$

$$H_2N(CH_2)_6NHC(=NH)NHNO_2$$

(117)

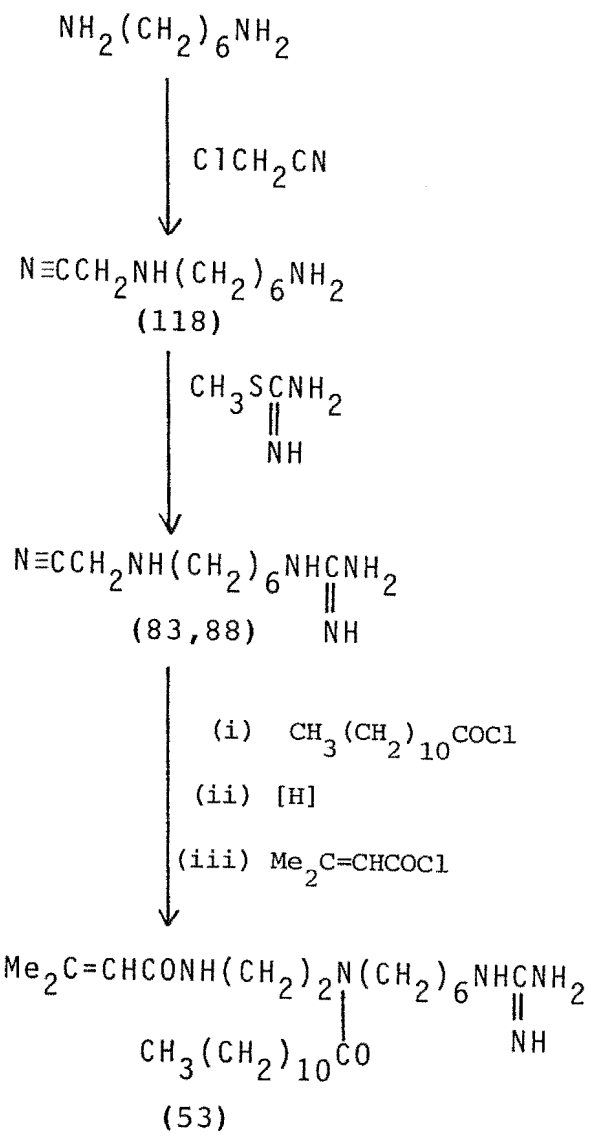
Concurrent with the attempted protection of the primary amine of aminohexylguanidine (74) in Scheme IX the protective groups were reacted with diaminohexane. The acylation reactions with diaminohexane are described in Sections 2.5 and 2.6 (Scheme XII).

2.4 From Alkylated 1,6-Diaminohexane

As aminohexylguanidine (74,84,87) could not be alkylated, a variation of Scheme V, which delayed the amidination step, was investigated. The variant described in Scheme X, is an approach in which selective amidination of the primary amine in the presence of a secondary amine was attempted[10].

2.4.1 From Chloroacetonitrile

Equimolar quantities of chloroacetonitrile (79) and diaminohexane were heated at reflux with potassium carbonate in benzene. The oil contained a mixture of the


NH2(CH2)6NH2
ClCH2CN
N≡CCH2NH(CH2)6NH2
(118)
CH3SCNH2
NH
N≡CCH2NH(CH2)6NHCNH2
NH
(83,88)
(i) CH3(CH2)10COCl
(ii) [H]
(iii) Me2C=CHCOCl
Me2C=CHCONH(CH2)2N(CH2)6NHCNH2
CH3(CH2)10CO
NH
(53)

SCHEME X

monocyanomethyl product (118) with small amounts of the unreacted diamine and the 1,6-bis(cyanomethyl) compound. Elution column chromatography, ion exchange chromatography and distillation (0.5 mm) failed to purify the cyanomethylamine (118), but dry column chromatography afforded pure amine (118).

Once purified, the amine (118) was reacted with a suspension of S-methylisothiouronium sulphate (75) in ethanol in an attempt to form the secondary amine (83). No reaction was observed at room temperature and little reaction was apparent after heating at reflux. The reaction was repeated in aqueous solution with stirring overnight followed by heating at reflux. After the solution had been heated, four compounds showing positive Sakaguchi tests were observed. The major component was isolated by ion exchange chromatography but the spectroscopic data did not indicate the presence of a nitrile group.

The amine (118) was heated to reflux in ethanol and treated with the pyrazole (76). The residue did not show a nitrile infrared absorption but a peak at 115 ppm, characteristic of a nitrile carbon, was evident in the ^{13}C n.m.r. spectrum. The cyanomethylamino methylene was not observed by n.m.r.

After the failure with S-methylisothiouronium sulphate (75) and ambiguous results with the pyrazole (76) method, the reaction was repeated using the ethanol soluble S-methylisothiouronium iodide (119). The iodide (119)

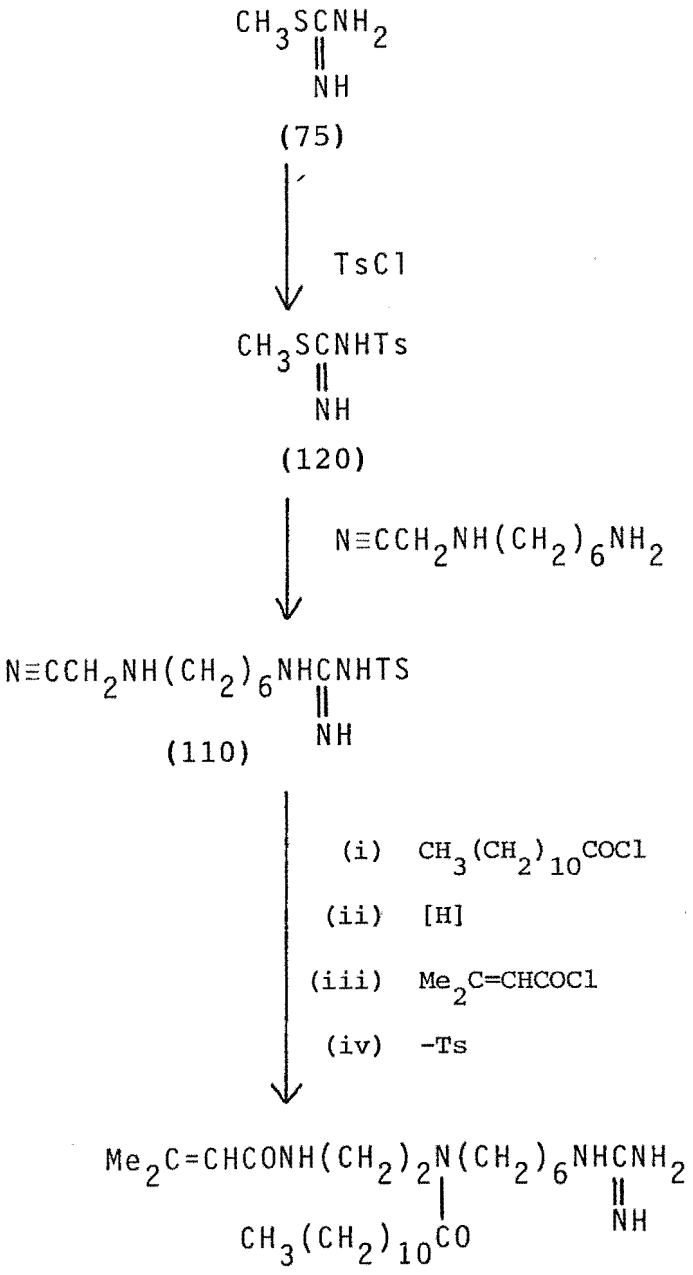
was readily prepared from the sulphate (75) by heating the sulphate (75) at reflux in ethanolic sodium iodide solution[64]. An ethanol solution of the amine (118) and the iodide (119) stirred overnight afforded two compounds giving positive Sakaguchi tests. The compounds were not separable by dry column chromatography and hydrolysis of the nitrile occurred during ion exchange chromatography (n.m.r.). The guanidinium compound (88) was not identified.

2.4.2 From N-(*p*-Toluenesulphonyl)-S-methylisothiourea

It is considered that the series of reactions described above all failed because of the difficult conditions created by the ionic and polar functionalities. In some cases, no reaction occurred and in other cases purification proved to be impossible.

The direction thus taken was a consequence of attempts to neutralize the guanidine group. As described in Section 2.3, if the guanidine was deactivated subsequent reactions and chromatography could be undertaken in less polar solvents. This method utilized a sulphonated thiourea.

The following scheme (Scheme XI) was proposed.


CH3SCNH2
NH
(75)
TsCl
CH3SCNHTs
NH
(120)
N≡CCH2NH(CH2)6NH2
N≡CCH2NH(CH2)6NHCNHTS
NH
(110)
(i) CH3(CH2)10COCl
(ii) [H]
(iii) Me2C=CHCOCl
(iv) -Ts
Me2C=CHCONH(CH2)2N(CH2)6NHCNH2
CH3(CH2)10CO
NH
(53)

SCHEME XI

If the isothiourea (75) could be neutralized by sulphonation in the initial reaction, then the primary amine (118) would be guanidinated by the N-(*p*-toluenesulphonyl)-isothiourea (120) to form the protected guanidine (110). The subsequent reactions would be the same as the relevant reactions described in Scheme IX (Section 2.3.5). Deprotection of the guanidine could be left until the last step.

N-(*p*-Toluenesulphonyl)-S-methylisothiourea (120) was prepared by addition of tosyl chloride and aqueous sodium hydroxide independently and simultaneously to a stirred aqueous solution of the isothiourea (75)[65]. The product (120) was isolated in only 6% yield. Changing the base to sodium carbonate and sodium bicarbonate did not improve the yield. A Schotten-Baumann reaction with benzene as the organic phase improved the yield to 22%. No reaction occurred when triethylamine or pyridine were used. Reaction of the N-tosylisothiourea (120) with the amine (118) however did not occur, even after 3 days of stirring in ethanol.

Other more facile compounds related to the thiourea (120) have been reported by Rapoport[18] and Ferris[66]. Rapoport reported that in situations in which reactions with the N-tosylisothiourea (120) did not occur, good yields were achieved with dimethyl [(*p*-toluenesulphonyl)-imino]dithiocarbonate (121) and methyl [(*p*-touenesulphonyl)-imino](chloro)thiocarbonate (122)[18,67].

$(MeS)_2C{=}NTs$ (121)

$MeSC(Cl){=}NTs$ (122)

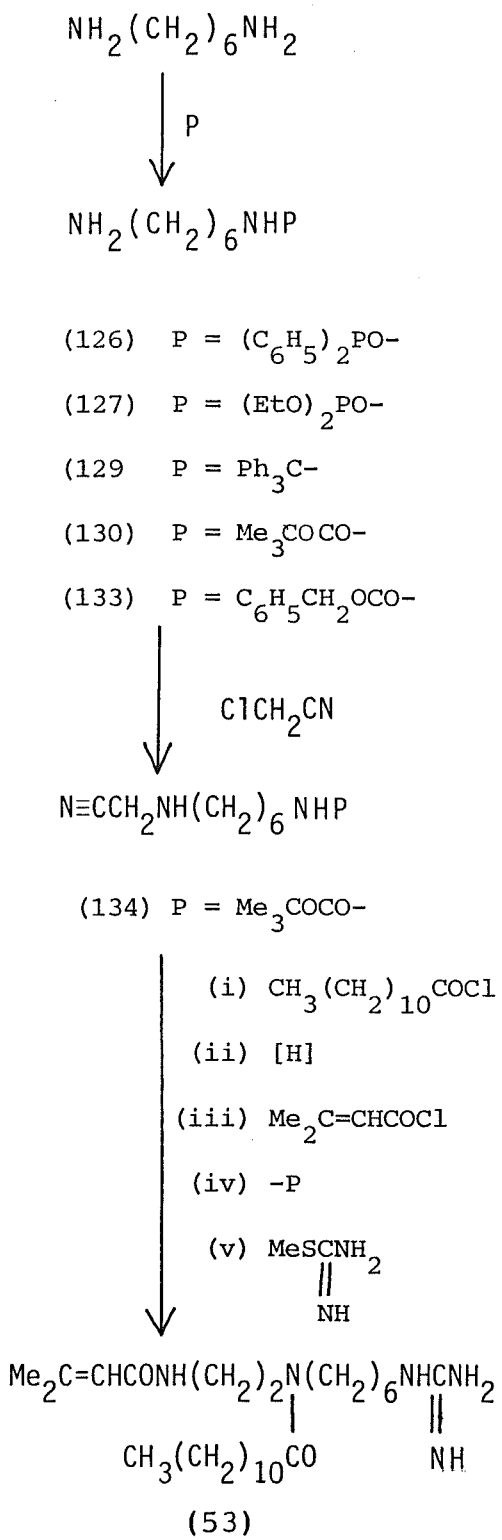
As these compounds were not available this direction was not pursued, however if all other methods failed the thiocarbonate method would warrant further investigation.

2.5 From Monoprotection of 1,6-Diaminohexane : N-P Bond Formation and N-C Bond Formation

As the guanidine group could not be prepared from the N-tosylisothiourea (120) in the first step, the proposal that guanidination be left to the last step was reconsidered (compare Schemes III and XII).

As the starting compound was 1,6-diaminohexane, protection of one of the amino groups was required to allow subsequent alkylation followed by acylation to occur exclusively at the requisite amine according to Scheme XII.

The protective groups available were diphenylphosphinyl chloride (54), diethyl chlorophosphate (66) and triphenylchloromethane (123). Although synthesis *via* the amide (71) had failed, differences in the reactivities of the phosphorus and alkyl compounds might have been great enough to allow the reactions (Scheme XII) to work. The three protective groups are all acid labile thus any one would be suitable for the synthesis. The triphenylmethyl(trityl) group can be cleaved by catalytic hydrogenation, therefore an alternative approach to the reduction of the nitrile might have been required, as the reduction would establish two primary amines.



(53)

SCHEME XII

2.5.1 From the Diphenylphosphinyl and Diethoxyphosphoryl Protective Groups

The protection of an amino group of diaminohexane with the phosphorus compounds (54) and (66) was attempted in dichloromethane at 0°. The 1,6-bis(diphenylphosphinamide) (124) was isolated and identified by n.m.r. and from the reaction using diethyl chlorophosphate (66) a compound tentatively identified as the 1,6-bis(phosphoramidate) (125) was isolated. The phosphorus compounds were at least as reactive as acyl halides and the monoprotected compounds (126) and (127) were not observed.

2.5.2 From the Triphenylmethyl Protective Group

Alkylation with triphenylchloromethane at 0° in chloroform solution afforded the 1,6-bis(trityl) derivative (128) as the major product and the monoalkylated compound (129) as a minor product which was not isolated but was identified by ^{13}C n.m.r. The bis-alkylation by the trityl group was contrary to the result of alkylation by chloroacetonitrile (79), but then chloroacetonitrile (79) is considerably less reactive.

$$PNH(CH_2)_6NHP'$$

(124) P=P'=$(C_6H_5)_2PO$-

(125) P=P'=$(CH_3CH_2O)_2PO$-

(126) P=$(C_6H_5)_2PO$-; P'=H

(127) P=$(CH_3CH_2O)_2PO$-; P'=H

(128) P=P'=$(C_6H_5)_3C$-

(129) P=$(C_6H_5)_3C$-; P'=H

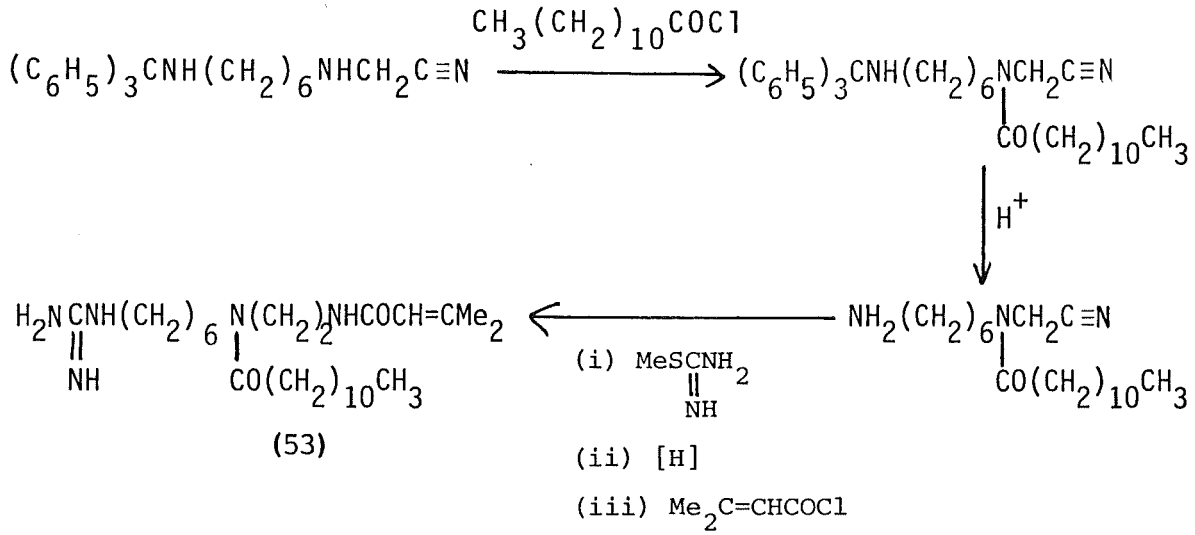
As the bulk of the trityl group inhibits reaction at the associated secondary amine compared to primary amines, tritylation of N-(cyanomethyl)-1,6-diaminohexane (118) to form the secondary amine (130) was attempted at 0° in chloroform. An intractable mixture precipitated out of solution.

$$(C_6H_5)_3CCl + NH_2(CH_2)_6NHCH_2C{\equiv}N \longrightarrow (C_6H_5)_3CNH(CH_2)_6NHCH_2C{\equiv}N$$

(118) (130)

Work up of the product was very difficult and the ease of removal of the trityl group during reduction of the nitrile posed other problems so this scheme was not pursued.

To overcome the problem created by the reduction, the following reactions were proposed. The failure of selective alkylation of the primary amine (118) prohibited further study into this method. 18-Crown-6 as a complexing agent for primary amines would be a viable alternate[68]. However, the crown ether was not available.



(53)

2.6 From Monoprotection of 1,6-Diaminohexane : Carbamate Bond Formation

A problem of earlier syntheses (*vide supra*) with the diaminoalkanes was that even if a monoprotected diamine was prepared in low yield it was part of an intractable mixture. The carbamate protective group is known for its substantial effect on the solubility properties of amines so isolation should be readily accomplished[18,26].

2.6.1 Monoprotection of 1,6-Diaminohexane

The mixed carbonate (97) was reacted with 1,6-diaminohexane in dioxan to afford N-(*tert*-butyloxycarbonyl)-1,6-diaminohexane hydrochloride (131) in 58% yield[26] (Scheme XI).

Although the monoprotected diaminohexane (131) had been prepared, an attempt was made to react benzyl chloroformate (94) with diaminohexane. The objective was to simplify the protection requirements as the preparation of benzyl chloroformate (94) was straightforward compared to the preparation of the mixed carbonate (97). Diaminohexane was treated with benzyl chloroformate (94) in both aqueous solution (Schotten-Baumann) and in dichloromethane, but in both cases the 1,6-bis(benzylcarbamate) (132), rather than N-(benzyloxycarbonyl)-1,6-diaminohexane (133), was isolated [Rapoport prepared N-(benzyloxycarbonyl)-1,2-diaminoethane (134) in 54% yield from benzyl chloroformate[18]].

$C_6H_5CH_2OCONH(CH_2)_2NH_2$

(134)

2.6.2 From the *tert*-Butyloxycarbonyl Group

The preparation of monoprotected diaminohexane (131) allowed several schemes to be considered. One approach to the total synthesis is described in Scheme XII.

Cyanomethylation in ethanol with inorganic base, according to the method of Sidhu *et al.*[47], led to many decomposition products. The side reactions were attributed to the acid catalysed hydrolysis of the *tert*-butyloxycarbonyl group being more rapid than the two phase reaction of the released hydrogen chloride with the solid inorganic bases. When triethylamine was used as the base, there was no reaction at room temperature (contrary to cyanomethylation of 1,6-diaminohexane). In a benzene solution heated at reflux very slow reaction occurred, but in refluxing ethanol the alkylation was completed within 4h to yield N-(*tert*-butyloxycarbonyl)-N'-cyanomethyl-1,6-diaminohexane (135).

Also, the primary amine (131), when converted to the free base, reacted readily with acrylonitrile (55) in a Michael addition at room temperature to again form N-(*tert*-butyloxycarbonyl)-N'-cyanoethyl-1,6-diaminohexane (136).

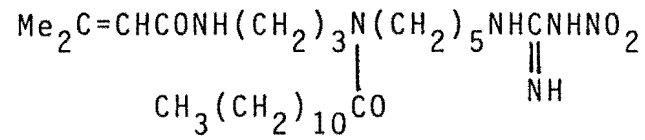
The two alkylation reactions suggested that the synthesis of acarnidines by Scheme XII is feasible as the nitrile can be reduced in the presence of amides and reputedly in the presence of the *tert*-butyloxycarbonyl group. Concurrent with this approach other reactions which led to the successful synthesis of the acarnidines

were being attempted (Section 3 of the Discussion).

2.7 Conclusion

The incorporation of the guanidine at the first step was a method that immediately proved to be unsuccessful (Schemes V and VIII). Protection of the guanidine with the isobornyloxycarbonyl group was unsatisfactory and the benzyl carbamate could not be hydrogenolysed quantitatively (Scheme IX). The third method, which incorporated the *p*-toluenesulphonyl group for protection and deactivation of the guanidino group, conferred unusual and unexpected stability onto the amine, although alkylation was possible in low yields (Scheme IX).

Vindication for the discontinuation of the synthesis of the acarnidine (53), by preliminary protection of the guanidino group, has recently been provided. The failure of a group at the University of Warwick (England)[69] to deprotect the guanidino group of the acarnidine precursor (137), in a scheme related to Scheme XIII (*vide infra*) prevented their reporting a successful total synthesis simultaneously with the one described in this thesis (Scheme XIII)[70]. The English team had protected the guanidine with the nitro group.



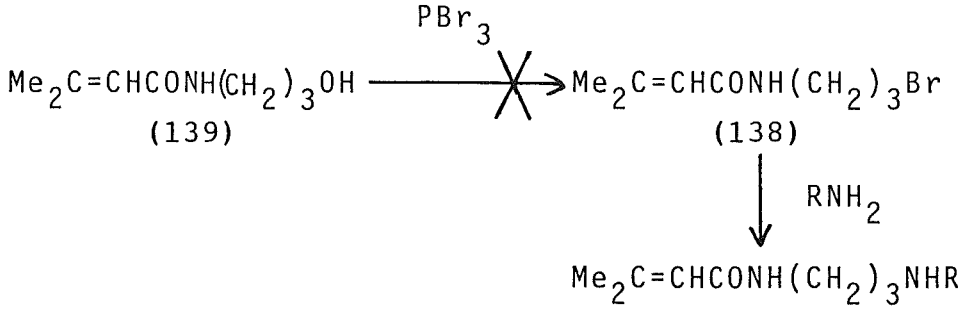
(137)

3. SYNTHESIS OF THE ACARNIDINES

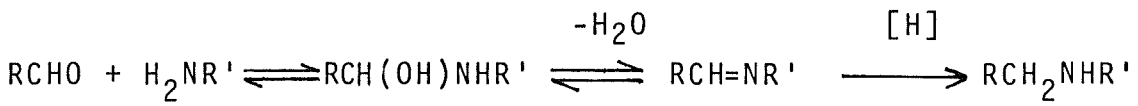
3.1 Convergent Syntheses and Reductive Alkylation

In all of the attempted syntheses of the acarnidines so far, the reactions that utilized the monoprotected diaminohexane (131) appeared to be most suitable for the total synthesis. The monoprotected diaminohexane (131) also lent itself to a convergent synthesis.

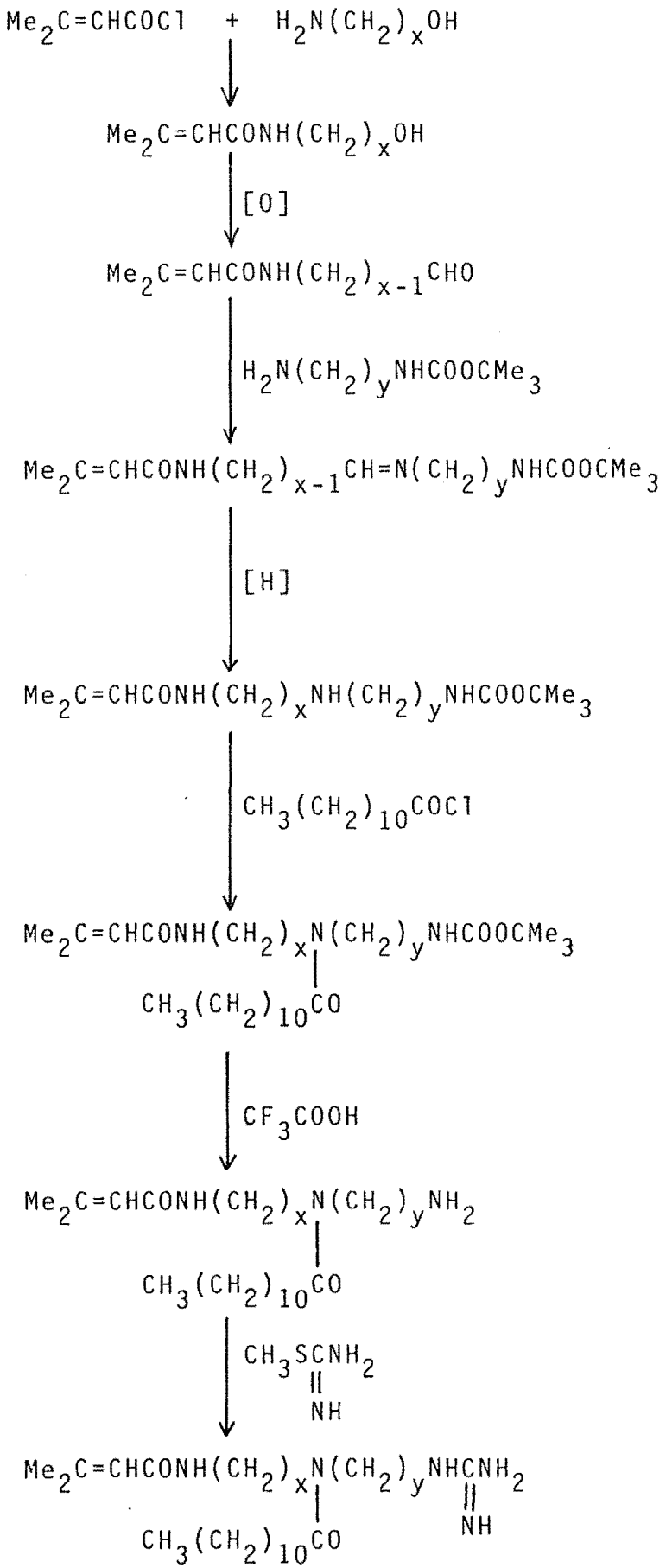
Gottschalk[8] had been unable to prepare the alkyl halide N-(3-bromopropyl)-3,3-dimethylacrylamide (138) from the alcohol (139) preventing the normal alkylation of an amine by an alkyl halide (see Scheme VII).



An alternative approach to the coupling reaction would therefore be by oxidation of an alcohol to the aldehyde followed by reductive alkylation *in situ* to afford the secondary amine[71-73]. This approach relates to the retrosynthetic analysis in which A = OH, B = NH_2 and D = NHP (see p. 22). X and y correspond to 3 and 5 respectively for the natural product.



The total synthesis would evolve according to Scheme XIII.


Me2C=CHCOCl + H2N(CH2)xOH
Me2C=CHCONH(CH2)xOH
[O]
Me2C=CHCONH(CH2)x-1CHO
H2N(CH2)yNHCOOCMe3
Me2C=CHCONH(CH2)x-1CH=N(CH2)yNHCOOCMe3
[H]
Me2C=CHCONH(CH2)xNH(CH2)yNHCOOCMe3
CH3(CH2)10COCl
Me2C=CHCONH(CH2)xN(CH2)yNHCOOCMe3
CH3(CH2)10CO
CF3COOH
Me2C=CHCONH(CH2)xN(CH2)yNH2
CH3(CH2)10CO
CH3SCNH2
NH
Me2C=CHCONH(CH2)xN(CH2)yNHCNH2
CH3(CH2)10CO
NH

SCHEME XIII

Apart from the amidination of the primary amine in the last step of Scheme XIII, the main feature was the efficacy of the reductive alkylation. Traditionally, equal quantities of amine and carbonyl compounds are mixed in an equilibrium reaction. To ensure the amine is formed, water is removed by azeotropic distillation, by addition of a suitable drying agent (sodium sulphate, potassium carbonate, potassium hydroxide or molecular sieves), or by addition of a Lewis acid (titanium tetrachloride). Once formed, the imine (Schiff base) could be reduced by catalytic hydrogenation or by the addition of an aluminium- or boronhydride. Some of the methods were eliminated from consideration; for example strong base or titanium tetrachloride could hydrolyse the amide or carbonate groups and catalytic hydrogenation is laborious compared to the relatively mild reducing agent sodium borohydride. Furthermore, sodium borohydride should not attack the N-carbonyl groups.

The model chosen to test the proposed alkylation was a reaction of propanal with one mole equivalent of aminobutane in the presence of molecular sieves followed by a sodium borohydride reduction.

$$CH_3CH_2CHO + H_2N(CH_2)_3CH_3 \rightleftharpoons CH_3CH_2CH{=}N(CH_2)_3CH_3 \xrightarrow{NaBH_4} CH_3(CH_2)_2NH(CH_2)_3CH_3 \quad (140)$$

The coupling was performed in tetrahydrofuran at room temperature. The loss of the aldehyde proton and gain of the imine proton were readily observed by ^1H n.m.r. of the reaction solution. When the formyl proton was no longer

observed (12 min) the solution was filtered. After filtration and evaporation the imine was reduced to a secondary amine (140) by sodium borohydride in ethanol in good yield, establishing the viability of this method. No attempt was made to isolate the imine as Schiff bases formed from aldehydes and primary amines are reputed to be very unstable[74].

The simplest route to the acarnidines (1) utilizing reductive alkylation is described in Scheme VI. However, a model reaction using propanal and aminohexylguanidinium tetraphenylborate (84) in tetrahydrofuran in an attempt to prepare N-(6-propylaminohexyl)guanidine (141) was unsuccessful. A polar, unidentified compound was isolated.

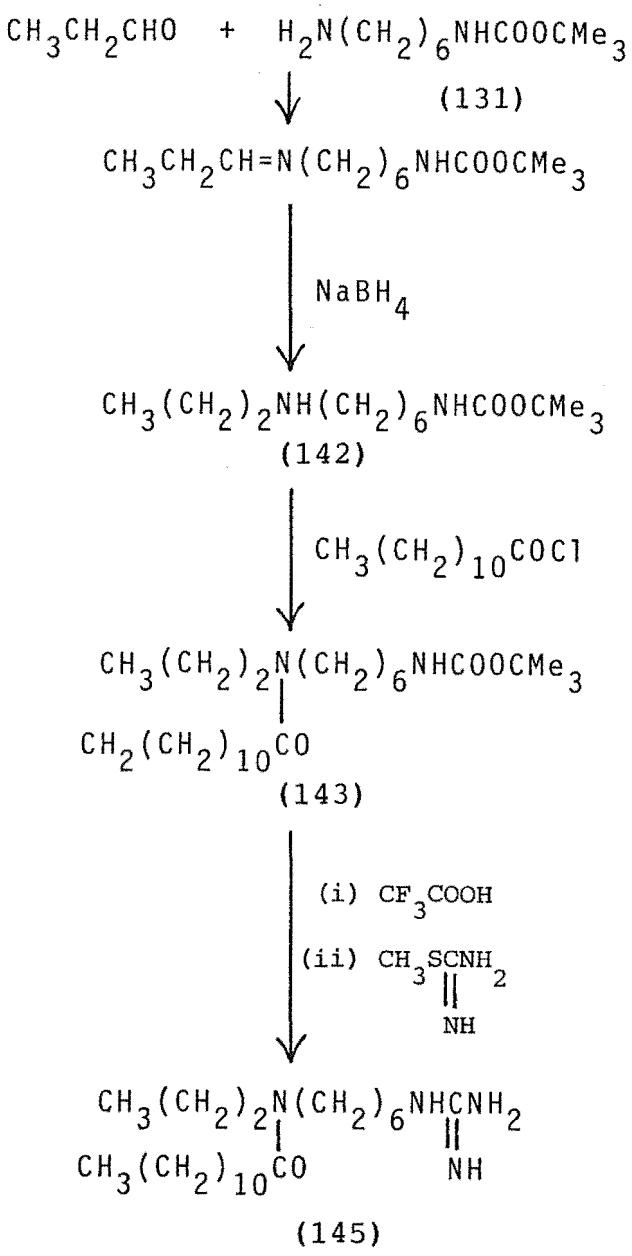
$$CH_3(CH_2)_2NH(CH_2)_6NHC(=NH)NH_2$$

(141)

3.2 A Model Acarnidine Synthesis

The other route to the acarnidines (1) *via* a Schiff base (Scheme XIII) involved a monoprotected diamine. Again a model reaction was chosen (Scheme XIV). Propanal and the aminium chloride (131) were mixed in chloroform over molecular sieves and potassium carbonate.

The reaction was monitored by ^1H n.m.r. and after 4 h the aldehyde formyl proton was no longer observed. The solution was filtered and evaporated, then dissolved in a ethanolic solution of sodium borohydride and heated at reflux for 0.5 h. The product, N-(*tert*-butyloxycarbonyl)-N'-propyl-1,6-diaminohexane (142), was isolated in quantitative yield.


CH3CH2CHO + H2N(CH2)6NHCOOCMe3
(131)
CH3CH2CH=N(CH2)6NHCOOCMe3
NaBH4
CH3(CH2)2NH(CH2)6NHCOOCMe3
(142)
CH3(CH2)10COCl
CH3(CH2)2N(CH2)6NHCOOCMe3
CH2(CH2)10CO
(143)
(i) CF3COOH
(ii) CH3SCNH2
NH
CH3(CH2)2N(CH2)6NHCNH2
CH3(CH2)10CO
NH
(145)

SCHEME XIV

After the success of the coupling reaction, the remaining reactions in Scheme XIV were attempted. To maintain an analogy with the natural product (1a), the secondary amine (142) was acylated with dodecanoyl chloride (113) in dichloromethane with triethylamine as base. N-[6-(*tert*-butyloxycarbonylamino)hexyl]-N-propyldodecanamide (143) was isolated in 93% yield. Neither the preparation of the secondary amine (142) nor the amide (143) required chromatographic purification. Hydrolysis of the carbamate (143) by swirling for 50 min in trifluoroacetic acid at room temperature afforded the amine as the trifluoroacetate (144.CF_3COOH)[75]. Spectroscopic analysis was simplified by conversion of the salt to the free base (144) which was recovered in 93% yield. Minor impurity peaks due to unsaturated carbons were observed in the ^{13}C n.m.r. spectrum and a minor infrared absorption was detected at 1725 cm^{-1} [C=O(carbamate) 1710 cm^{-1}]. No impurity was detected by ^{1}H n.m.r.

Most of the amine (144) was committed to reactions with S-methylisothiourea. Attempted reaction with S-methylisothiouronium sulphate (75) in water at room temperature and at reflux in ethanol produced several products which were not isolated. Reaction at room temperature with S-methylisothiouronium iodide (119) in ethanol afforded N-(6-guanidinohexyl)-N-propyldodecanamide (145) in 82% crude yield. The guanidine (145) was subsequently purified by gel permeation chromatography (*vide infra*) in a 37% yield. The major impurity was

was positive to the ninhydrin test. The 37% yield of pure compound (145) belied the fact that considerable tailing occurred with the guanidine (145) which prevented greater recovery of pure compound (145). After gel permeation chromatography the infrared spectrum of the product no longer showed the peak at 1725 cm^{-1}.

The success of this scheme was enhanced by the high yields recovered from each reaction. Another advantage was that chromatography could be left to the last step satisfying the optimum conditions sought for a good synthesis, as described in the Introduction (1.4). After the successful preparation of the model propyl compound (145), the synthesis of the 2,6-acarnidine (53) came closer to being a reality.

3.3 Synthesis of a 3,6-Acarnidine

3.3.1 Preparation and oxidation of an amido-alcohol.

The initial requirement of Scheme XIII was the need to prepare the appropriate amido-alcohol before oxidation to the aldehyde. By the usual acylation method 3,3-dimethylacryloyl chloride (56) was added slowly to a chilled solution of 2-aminoethanol in chloroform. Evidence that 2-(hydroxypropyl)-3,3-dimethylacrylamide (146) was water soluble was revealed by the low recovery of the amide (146) after the normal water/chloroform work up. A higher yield of the amide (146) was achieved by the addition of 2-propanol to the chloroform and by the use of

aqueous acid and base solutions saturated with brine. The amide (146) was immiscible with ether.

If a trace of water was present during the acylation reaction, the proportion of ester product was significant. The ester, O-[2-(3,3-dimethylacrylamido)ethyl] 3,3-dimethylacrylate (147) could be readily hydrolysed to the amido-alcohol (146) with methanolic sodium hydroxide.

$Me_2C{=}CHCONH(CH_2)_2OH$ (146)

$Me_2C{=}CHCONH(CH_2)_2OCOCH{=}CMe_2$ (147)

Oxidation of the alcohol (146) to N-(2-oxoethyl)-3,3-dimethylacrylamide (148) could not be achieved in a satisfactory yield. Attempted oxidation with chromium compounds generally over-oxidized the alcohol to the acid or to many unidentified products. An infrared absorption at *ca* 2250 cm^{-1} was diagnostic of the aldehyde as the aldehyde carbonyl absorption is almost identical to an acid carbonyl absorption. For some of the reactions, the high polarity of the alcohol may have contributed to the low yields as removal of the chromium salts was difficult.

Oxidations with Jones' reagent[76], chromium trioxide-pyridine[77], pyridinium chlorochromate[78] (also attempted on alumina)[79], chromium trioxide in HMPA[80], potassium dichromate in dimethylsulphoxide and sulphuric acid[81], and *tert*-butyl chromate[82] were all attempted without success.

Pyridinium chlorochromate produced the aldehyde but it was isolated in admixture with the carboxylic acid (confirmed by deuterium exchange in the ^{1}H n.m.r. spectrum).

Although it would have been very expensive on a large scale, a silver carbonate oxidation (Fétizon)[83] was attempted but it also did not succeed. A consideration with silver carbonate oxidations is the possibility that the double bond in the alcohol (146) may be vulnerable to attack or complexation by the silver ion[83].

The third class of oxidation reactions was based on dimethylsulphoxide (the Moffat oxidation[84] and related reactions). The Moffat oxidations with dicyclohexylcarbodiimide and pyridinium trifluoroacetate[85], orthophosphoric acid and sulphur trioxide[86] produced non-polar and/or intractable products that were not identified.

Oxidation with the dimethylsulphoxide/oxalyl chloride complex[87] afforded the aldehyde (148) as 30% of a mixture isolated in 53% yield. The aldehyde (148) rapidly decomposed.

The last oxidation method attempted was by means of N-chlorosuccinimide and thioanisole[88]; however, after extraction no formyl protons were detected by ^{1}H n.m.r.

As so many oxidative techniques were attempted without success, proof that there was no fault in the methodology was accomplished by oxidation of octanol.

$$CH_3(CH_2)_6CH_2OH \xrightarrow{[O]} CH_3(CH_2)_6CHO$$

(150)

Whereas Jones' reagent oxidized octanol quantitatively to octanoic acid (149), *tert*-butyl chromate, pyridinium chlorochromate and dimethylsulphoxide/oxalyl chloride all oxidized octanol to octanal (150).

Attempts to oxidize the alcohol (146) were suspended in favour of reactions based on its homologue N-(3-hydroxypropyl)-3,3-dimethylacrylamide (139). The amidopropanol (139) prepared from 3-aminopropanol by the usual acylation method, required the same work up procedures as the water soluble amidoethanol (146). When the ester was formed as a byproduct it was readily hydrolysed in a 10% sodium hydroxide/methanol solution heated at reflux for four minutes.

Oxidation of the amidopropanol (139) to N-(3-oxopropyl)-3,3-dimethylacrylamide (151) was successfully accomplished with dimethylsulphoxide/oxalyl chloride in 78% yield. The complex was prepared at -70° by the rapid addition of dimethylsulphoxide to a solution of oxalyl chloride in dichloromethane. The alcohol was then added and after 15 min the reaction was quenched with triethylamine. As for the alcohol (139), extraction from a saturated aqueous brine wash was required. The aldehyde (151) was about 85% of a mixture which substantially decomposed after standing overnight at 4° (^{1}H n.m.r.). However, when it was purified by column chromatography, the aldehyde (151) was stable for longer periods. In most preparations of the aldehyde (151), the purity was high enough to use without further purification. Purity

was estimated by comparison of the formyl proton integral to the proton integrals of other ^{1}H n.m.r. peaks. As a check on the efficiency of the dimethylsulphoxide/oxalyl chloride oxidation, the oxidation was attempted with *tert*-butyl chromate. The aldehyde (151) was not identified.

The successful oxidation of the amidopropanol(139) thus opened the possibility for the complete synthesis of the acarnidines and established a general synthetic route. The subsequent reactions in the scheme were built upon the previous success of the method based on propanal (Schemes XIII and XIV). To ensure the efficacy of the aldehyde method a complete synthesis was undertaken before other homologues of the alcohol (139) and N-(*tert*-butyloxycarbonyl)-1,6-diaminohexane (131) were prepared. This general method is described, followed by a description of subsequent successes and failures encountered in the synthesis of the acarnidines.

3.3.2 From Reductive Alkylation to the 3,6-Acarnidine

By the same technique as that described for the preparation of N-(*tert*-butyloxycarbonyl)-N'-propyl-1,6-diaminohexane (142), the freshly prepared aldehyde (151) was reacted with N-(*tert*-butyloxycarbonyl)-1,6-diaminohexane (131) in chloroform. After filtration, evaporation and reduction with sodium borohydride, the secondary amine N-(*tert*-butyloxcarbonyl)-N'-[3-(3,3-dimethylacrylamido)-propyl]-1,6-diaminohexane (152), was isolated in 72% yield. When the amine (131) was used as the aminium chloride

(131.HCl), the reaction rate was slow, according to the rate of formyl proton reduction (^{1}H n.m.r.). When the amine was used as the free base reaction was rapid and was complete within 0.5 h (^{1}H n.m.r.), although to ensure complete removal of water from the solution it was normally left for 1-2 h.

In a trial reaction, ethanol was used instead of chloroform with 3Å molecular sieves so that the filtration and evaporation steps could be eliminated. However, a lower yield was recorded.

Isolation of the secondary amine (152) from the reaction products was ultimately very simple. To ensure complete reaction of the primary amine (131) a sufficient excess of the crude aldehyde (151) was added to achieve approximately equal mole proportions of reactants. If an excess of aldehyde or amine was present further reaction could occur. Amines can react with Schiff bases in an aldol type condensation[74].

$$2RCH_2CH{=}NR' \longrightarrow R'NH_2 + RCH_2CH{=}\overset{\overset{R}{|}}{C}CH{=}NR'$$

Aldehydes, if in excess, can react with an amine to form tertiary amines during the reduction. Fortunately, sodium borohydride readily reduces aldehydes preventing this reaction from becoming significant. (Other, milder, reducing agents have been proposed; for example sodium cyanoborohydride[89] and tetraalkylammonium borohydrides[90] for selective reductions and in aprotic solvents).

Quantitative reaction of the primary amine (131) left only the secondary amino group sensitive to salt formation. After reduction, the ethanol was removed by evaporation and the residue was taken up in a little water and acidified with 1% aqueous hydrochloric acid. Extraction of the aqueous solution with ethyl acetate removed all of the neutral impurities. The aqueous solution was then saturated with sodium chloride and extracted with 5% 2-propanol/chloroform to afford the pure secondary aminium compound (152). Protonation of the amine was occasionally very slow and gummy mixtures of the salt and free base were isolated.

Acylation of the secondary amine (152) with dodecanoyl chloride (113) by the usual method afforded N-[6-(*tert*-butyloxycarbonylamino)hexyl]-N-[3-(3,3-dimethylacrylamido)propyl]dodecanamide (153) in 73% yield after chromatography on silica gel.

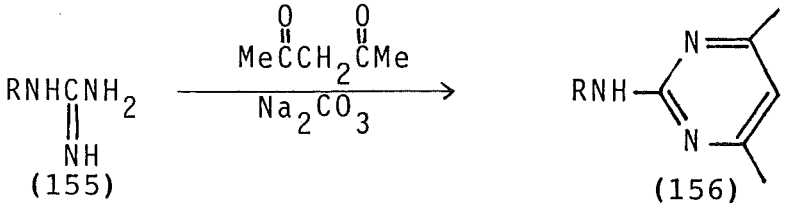
Hydrolysis of the carbamate (153) by neat trifluoroacetic acid in the same method as that used for the propylamide (143) afforded the primary amine, N-(6-aminohexyl)-N-[3-(3,3-dimethylacrylamido)propyl]dodecanamide (154) in high yield. The primary amine (154) was unstable at 4° and was therefore used immediately in the final reaction of the synthesis.

The final reaction was the amidination by S-methylisothiouronium iodide (119) at room temperature in ethanol for 24-36 h. For the first attempts at the guanidine preparation, after evaporation of the alcohol, the oil

was taken up in chloroform and washed with 2% aqueous hydriodic acid. The solution emulsified and the emulsion was only broken by saturation with sodium iodide. Therefore, in most of the reactions the extraction was accomplished by washing the chloroform solution with aqueous sodium iodide. Although the crude yield of the 3,6-acarnidine (155) was 93%, conclusive proof of its identity was difficult to obtain.

As it was an oil and a salt, micro analysis and high resolution electron impact mass spectrometric methods were unsuccessful. The acarnidine (155) was purified by gel permeation chromatography (*vide infra*).

To aid analysis, the acarnidine (155) was converted to the dimethylpyrimidine (156) by heating an aqueous ethanol solution of the 3,6-acarnidine (155) with 2,4-pentanedione and sodium carbonate.

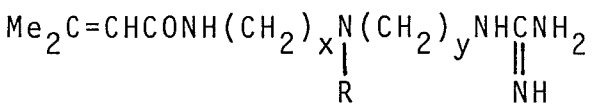


(155) (156)

Low resolution electron impact mass spectrometry (HP 5982A) afforded the parent ion, as well as a large number of daughter ions, either identical or differing by 14 a.m.u. (CH_2) from the mass spectrum previously recorded for the pyrimidinyl derivative of the natural product (1a)[7].

3.4 Preparation of the Series of Fatty Acyl Chlorides, Dimethylacrylamides and 1,5-Diaminopentane

With a successful synthesis of the 3,6-acarnidine (155) accomplished, the method was expanded to include a series of *tert*-butyloxycarbonyl protected amines, a series of amido-alcohols, three fatty acyl chlorides [dodecanoyl chloride (12.0)(113), octadecanoyl chloride (18.0)(157) and Z-9-octadecenoylchloride (18:1ω9)(158)] and acetyl chloride as described in the following diagram. Although unsaturation was present in the acarnidines (1b) and (1c) the relevant fatty acids were not prepared. Oleic acid was used as a compromise. The fatty acyl chlorides were prepared from the acids heated with thionyl chloride.



x = 2,3,4,5

y = 2,4,5,6

R = $-CO(CH_2)_{10}CH_3$ (12.0)

= $-CO(CH_2)_{16}CH_3$ (18.0)

= $-CO(CH_2)_7CH{=}CH(CH_2)_7CH_3$ (Z) (18:1ω9)

= $-COCH_3$ (2.0)

Not all combinations of x,y and R were attempted but examples representative of the variety of analogues were to be prepared.

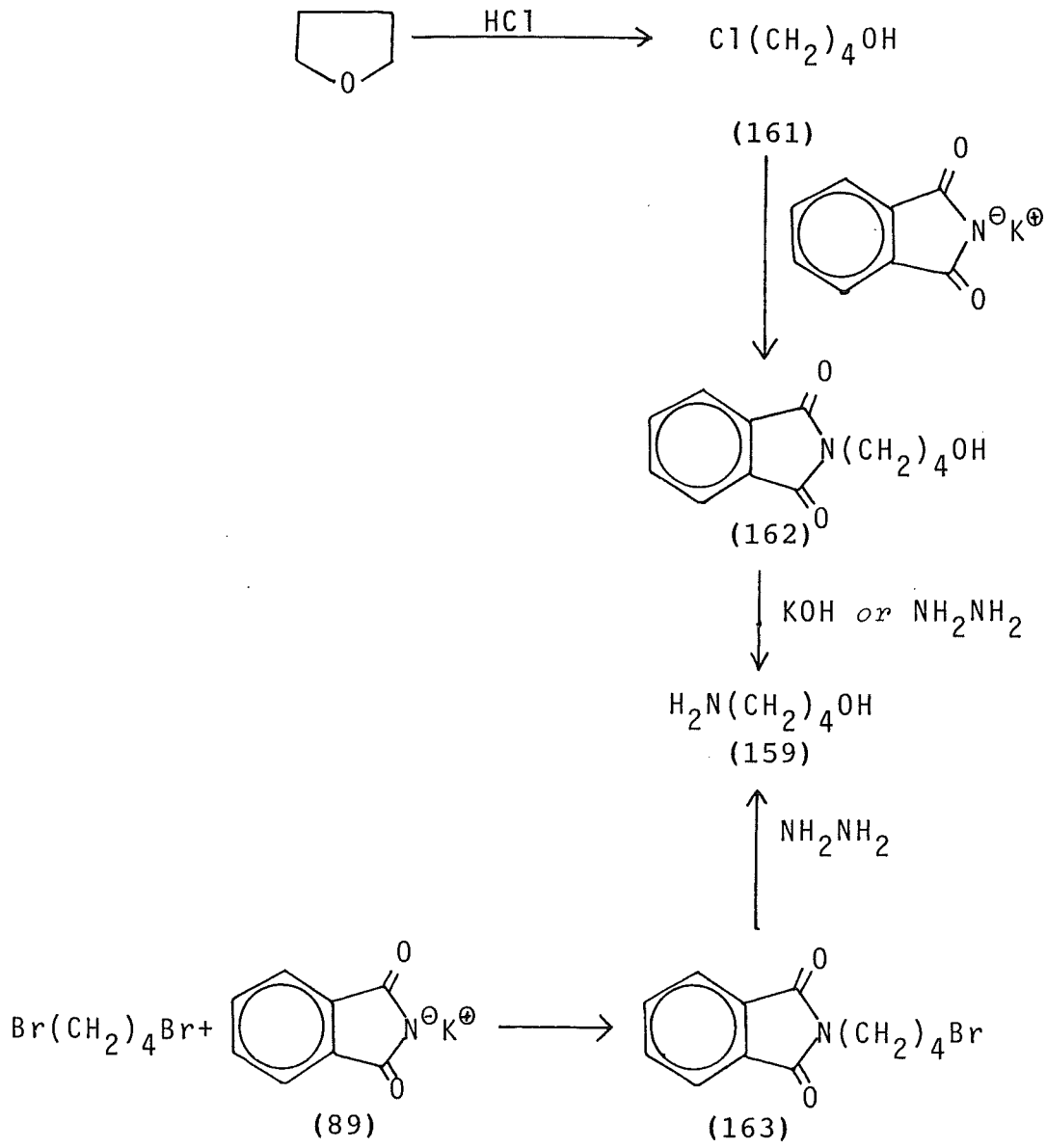
Two of the starting synthons, 4-aminobutanol (159) and 1,5-diaminopentane (160) needed to be prepared before

schemes based on x=4 and y=5 could be attempted.

Two approaches to the synthesis of 4-aminobutanol (159) were followed, according to literature methods. The first method began with ring opening of tetrahydrofuran with hydrogen chloride to form 4-chlorobutanol (161)[91]. The 4-chlorobutanol (161) was heated at 70° with potassium phthalimide (89) in dimethylformamide[92]. The phthalimidobutanol (162) was crystallized from a concentrated solution of chloroform after the dimethylformamide had been removed by distillation. The reactions were low yielding.

Two methods were used to isolate 4-aminobutanol (159). The phthalimidobutanol (162) was dissolved in a concentrated aqueous solution of potassium hydroxide and after two days the solution was distilled to dryness[93]. After cooling, more water was added to the residue and the distillation was repeated. In both distillations the initial slightly alkaline fractions were discarded. Careful removal of water by repeated distillation afforded 4-aminobutanol (159) in only 7% yield.

An alternative to the base hydrolysis of the phthalimidobutanol (162) is the hydrazine method devised by Sheehan and Bolhofer[94] which afforded 4-aminiobutanol chloride (159.HCl) in 85% yield. When the salt (159.HCl) was converted to the free base, by repeated distillation from potassium hydroxide, the yield was 10%.



The second approach to the 4-aminobutanol (159) was by reaction of 1,4-dibromobutane with potassium phthalimide (89)[95]. Bromobutylphthalimide (163) was isolated in 63% yield, but potassium hydroxide hydrolysis[93], as described for phthalimidobutanol (162), afforded 4-aminobutanol (159) in only 7% yield.

4-Aminobutanol (159) is extremely hygroscopic and forms an azeotrope with water during distillation.

Prolonged standing over potassium hydroxide pellets in a sealed bottle followed by distillation still did not afford the amine (159) in high yield. Codistillation with benzene to remove water also failed.

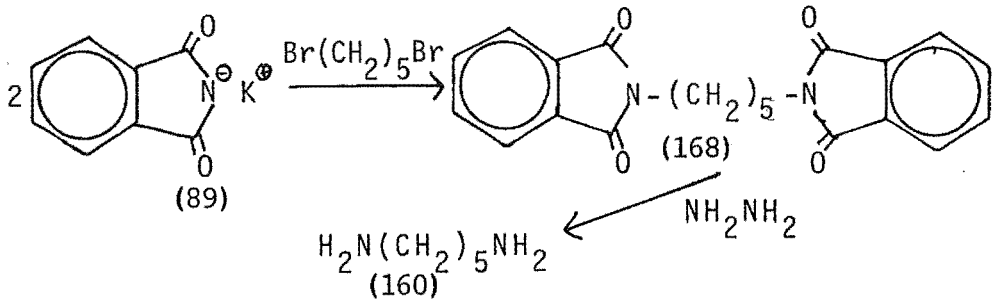
N-(4-Hydroxybutyl)-3,3-dimethylacrylamide (164) was prepared from 4-aminobutanol (159) by the usual acylation method, but even this reaction was low yielding. If a trace of water was present, 4-aminobutanol (159) became immiscible in chloroform at 0° (differing from 3-aminopropanol and 5-aminopentanol) and a high proportion of the ester would form. When the reaction was repeated in dimethylformamide the amido-ester was isolated in quantitative yield. In acetonitrile; however, the proportion of ester formation was minimal, even if moisture was not specifically excluded.

N-(5-Hydroxypentyl)-3,3-dimethylacrylamide (165) was prepared from 5-aminopentanol while N-(2,2-dimethoxyethyl)-3,3-dimethylacrylamide (166) was prepared from aminoacetaldehyde dimethylacetal (167) by the usual acylation method. The acetal (166) was prepared for an alternative route to the 2,6-acarnidine (53).

$$\underset{(56)}{Me_2C{=}CHCOCl} + \underset{(167)}{H_2NCH_2CH(OMe)_2} \longrightarrow \underset{(166)}{Me_2C{=}CHCONHCH_2CH(OMe)_2}$$

1,5-Diaminopentane (160) was prepared in a similar manner to that described for bromobutylphthalimide (163) except that two mole equivalents of potassium phthalimide (89) were reacted with 1,5-dibromopentane in dimethylformamide[94]. 1,5-Diphthalimidopentane (168) was recrystallised from

carbon disulphide. Hydrazinolysis afforded 1,5-diaminiopentane chloride (160.2HCl) in 89% overall yield. The free diamine (160) was obtained by distillation from a sodium hydroxide and soda-lime mixture followed by distillation from potassium hydroxide in 70% yield.



The homologues of the monoprotected diaminohexane (131) were prepared by the same literature method[26]. N-(*tert*-Butyloxycarbonyl)-1,5-diaminopentane (98) was isolated in 49% yield. N-(*tert*-Butyloxycarbonyl)-1,4-diaminobutane (170) and N-(*tert*-butyloxycarbonyl)-1,2-diaminoethane (171) did not precipitate from the aqueous solution when it was saturated with sodium chloride [as described for the protected diaminohexane (131)] and had to be extracted from the solution with 5% 2-propanol/chloroform. Yields of the recrystallized products were 65% and 38% respectively. Recently, Rapoport reported an alternative synthesis of N-(*tert*-butyloxycarbonyl)-1,2-diaminoethane (171)[18].

3.5 Acetal Hydrolysis and Alcohol Oxidation Leading to the Secondary Amines

Synthesis of the 2,6-acarnidine (53) starting from the amidoethanol (146) failed because the aldehyde (148) could not be prepared. Another route to the aldehyde (148) was based upon the hydrolysis of the acetal (166). The acetal group is a standard protective group used to mask the aldehyde function. Furthermore, acetals have been reacted directly with primary amines to afford the appropriate imine[72]. Attempts to prepare N-[9-(*tert*-butyloxycarbonylamino)hexyl]iminoethyl-3,3-dimethylacrylamide (172) with molecular sieves, with and without base, with and without solvent at room temperature and with heating, all failed.

$$\underset{(166)}{Me_2C{=}CHCONHCH_2CH(OMe)_2} + \underset{(131)}{H_2N(CH_2)_6NHCOOCMe_3} \not\rightarrow \underset{(172)}{Me_2C{=}CHCONHCH_2CH{=}N(CH_2)_6NHCOOCMe_3}$$

Hydrolysis of the acetal with dilute hydrochloric acid took 50 min at room temperature and a high yield of the aldehyde (148) was recovered in the presence of a small proportion of unreacted acetal (166). If the reaction was left longer an impurity rapidly formed.

$$\underset{(166)}{Me_2C{=}CHCONHCH_2CH(OMe)_2} \xrightarrow{H+} \underset{(148)}{Me_2C{=}CHCONHCH_2CHO}$$

The aldehyde (148) rapidly decomposed and it was therefore reacted with the primary amines without

purification by the same method as previously described for the amidopropanol (139) (Table I).

A reputedly very mild method of hydrolysing acetals has been reported. This method utilized a saturated solution of tartaric acid. Hydrolysis with tartaric acid failed.

N-(5-Hydroxypentyl)-3,3-dimethylacrylamide (165) was oxidized to the aldehyde (173) by the dimethylsulphoxide/oxalyl chloride method successfully and again it was reacted with the primary amines without purification (Table I).

N-(4-Oxobutyl)-3,3-dimethylacrylamide (174) was not prepared in a useful yield by the dimethylsulphoxide/oxalyl chloride method nor by Jones' oxidation. All attempts to prepare acarnidine analogues from 4-aminobutanol (159) were accordingly suspended.

The synthesis of the secondary amines based on the butyl- (170) and ethyl- (171) diamines failed by the usual method. Many attempts were made using purified aldehyde (151) and by adjustment of reaction times and reactant ratios. The problem was solved by lowering the temperature of the solutions of both the aldehydes and amines to ice temperature. All of the secondary amines that were prepared are described in Table I.

Unlike the rapid transacylation that occurred during the reaction of N-aminoethyl-3,3-dimethylacrylamide (71), there was no evidence that the *tert*-butyloxycarbonyl-compounds underwent any transacylation whatsoever in alkaline solution.

TABLE I : Reaction Yields of the Secondary Amines

$Me_2=CHCONH(CH_2)_xNH(CH_2)_yNHCOOCMe_3.HCl$

Compound	x	y	Yield (%)
142	(propyl)	6	100
152	3	6	73
175	3	5	71
176	3	4	79
177	3	2	80
178	5	5	63*
179	5	2	50
180	2	5	70
181	2	2	50

* This secondary amine was not isolated pure and it appeared to be unstable.

At this stage no attempt was made to prepare the 2,6-secondary amine.

As the ^{13}C chemical shifts of the secondary amines were ambiguous, a ^{13}C n.m.r. pH profile of the spermidine derivative (176) was compiled (Figure 1). Although the ^{13}C chemical shifts of spermidine (27) have been reported some overlap was apparent[97]. Carbon atoms α- and β- to a secondary amine, but especially the β-carbons, undergo a considerable upfield shift on formation of the amine salt[98]. Therefore, consideration of the pH induced

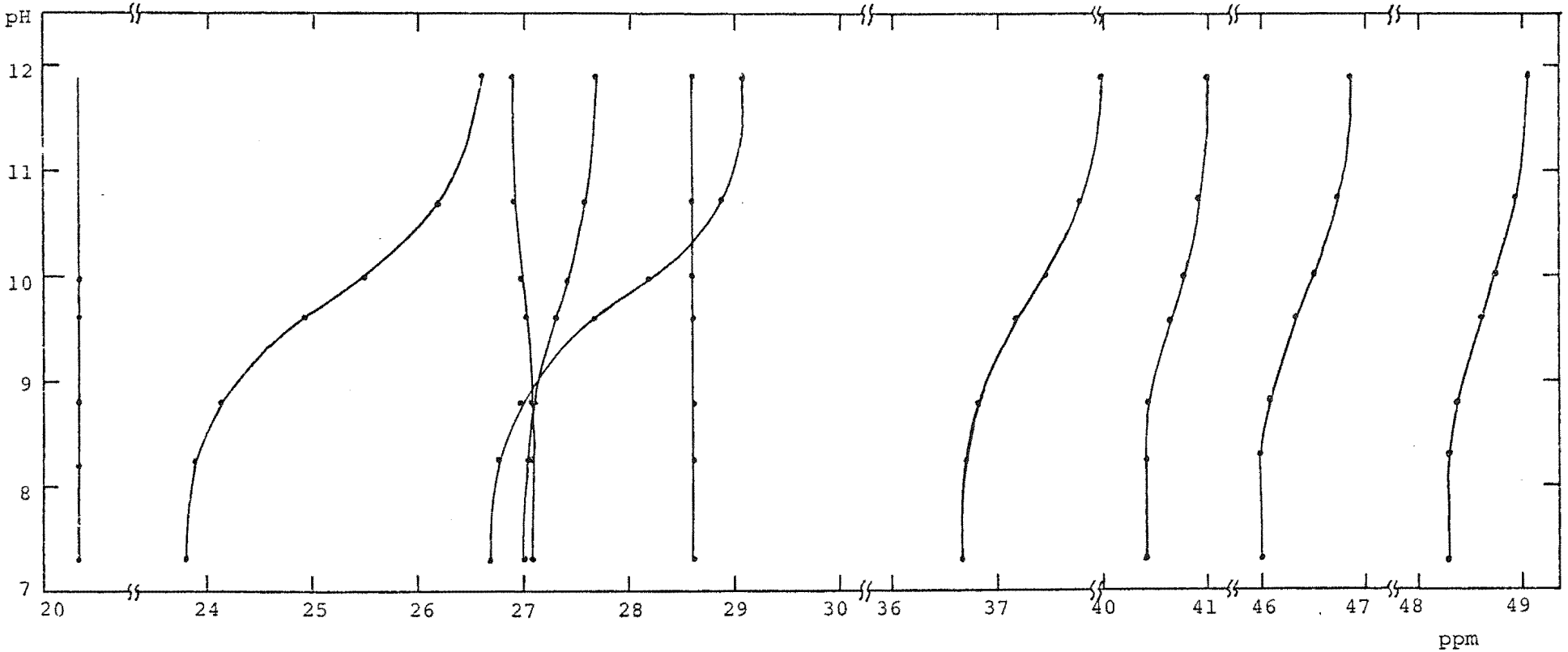


Figure 1 : pH Profile of N-(*tert*-Butyloxycarbonyl)-N'-[3-(3,3-dimethylacrylamido)propyl]-1,4-diaminobutane (176)

shifts and by comparisons with the peak shapes (C-α to the carbamate was broad) and locations of the carbon atoms in the other secondary amines, an unambiguous assignment could be made (Table II).

TABLE II : Maximum pH Induced ^{13}C n.m.r. Shifts (δ ppm)

$Me_2C=CHCONH-CH_2-CH_2-CH_2-NH-CH_2-CH_2-CH_2-CH_2-NHCOOCMe_3$							
pH 7.3	36.7	26.7	46.0	48.3	28.3	27.1	40.4
pH 11.9	38.0	29.1	46.8	49.1	26.6	28.6	41.0
Δδ	1.3	2.4	0.8	0.8	2.8	1.3	0.6

In all cases the unsaturated carbon chemical shifts in the ^{13}C n.m.r. were used to fingerprint the structures.

3.6 N,N-Disubstituted Amides

The next step in the synthesis of the acarnidines was the acylation of the secondary amines. The acylations with the requisite acyl chlorides were undertaken by the methods used in the preparation of the N,N-disubstituted amides (143) and (153). Not all of the amides needed to be purified by chromatography as the acylation reaction was practically quantitative; the main impurities being the appropriate acid resulting from hydrolysis of the acyl chloride. No unreacted amine was detected by t.l.c.

for those amides that were not chromatographed (Table III).

TABLE III : Reaction Yields of the Disubstituted Amides

$Me_2C=CHCONH(CH_2)_xNR(CH_2)_yNHCOOCMe_3$

Compound	x	y	R	Yield (%)
143	(propyl)	6	12.0	93*
153	3	6	12.0	73*
182	3	6	18.0	91*
183	3	6	18:1ω9	88*
184	3	5	2.0	76*
185	3	5	12.0	90*
186	3	5	18.0	92*
187	3	5	18:1ω9	91*
188	3	4	12.0	97
189	3	4	18.0	97
190	3	4	18:1ω9	98
191	3	2	12.0	98
192	3	2	18.0	98
193	3	2	18:1ω9	98
194	5	5	12.0	83*
195	5	2	12.0	75*
196	2	5	12.0	94
197	2	2	2.0	98
198	2	2	12.0	93*

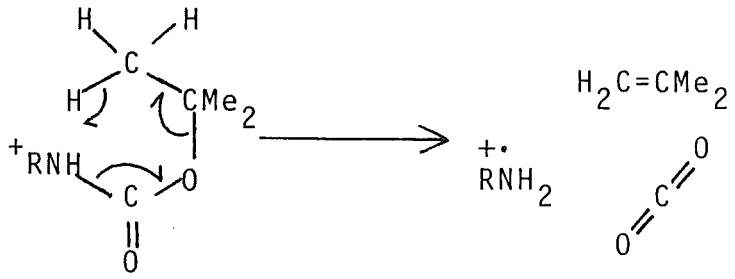
* The amide was purified by chromatography.

Exhaustive h.p.l.c. purification of the amide (185) was adequate for samples for micro analysis. This method did not lend itself, however, to the purification of all of the amides. A small shoulder to the major peak in the h.p.l.c. trace could not be resolved by changes in solvent, flow rates nor by fine cuts. Attempts to distil the amides at high vacuum (*ca.* 0.004 mm) did not lower the boiling point enough to prevent pyrolysis (b.p.>200°). The pyrolysis was noted by loss of the carbamate carbonyl peak (ν_{max} 1710 cm^{-1}) in the infrared spectra. Only the amide (233) was able to be purified by distillation [130-140°(0.004 mm)].

Confirmation of the identity of the N,N-disubstituted amides was gained by mass spectrometry. High resolution electron impact mass spectrometry failed to identify any molecular ions but two representative amides (154) and (185) were submitted for fast atom bombardment (f.a.b.) mass spectrometry. The sodiated molecular ions (MNa^+) were accurately measured (*vide infra*) and a low resolution spectrum was recorded for the natural product synthon (185). Major daughter ions resulting from the loss of butanol, carbon dioxide and isobutene from the quasi-molecular ion were recorded.

Chemical ionization mass spectrometry using isobutane was undertaken for all the amides and quasi molecular ions were detected for each one. The quasi molecular ion was transient, probably

as a consequence of the low volatility of the chemicals at one extreme and the thermal lability of the chemicals at the other. The spectrometer probe temperature when the quasi molecular ions were detected was in the range of 150-170°. The chemical ionization spectra also possessed fragmentation patterns from which most daughter ions could be identified. The most consistent peak was (MH^+-100) a.m.u. corresponding to loss of carbon dioxide and isobutene as observed by f.a.b.



A series of chemical ionization spectra were recorded for each amide so that the quasi molecular ion could be detected. The series indicated that the intensities of the daughter ions varied to a large extent preventing consistent peak intensity measurements. Chemical ionization spectra of the natural product synthon were also measured with the aid of ammonia gas. The spectra contained far fewer peaks than the isobutane spectra as expected but the (MH^+-100) a.m.u. peak was still prominent.

3.7 Carbamate Hydrolyses and the Acarnidine Preparations

Hydrolysis of the carbamates was achieved by following the method established for the preparation of the primary amines (144) and (154) (see Table IV). The amines decomposed when left for 3 days at 4° but transacylation was not apparent. The major decomposition product had a higher t.l.c. R_f yet was still a primary amine (positive to the ninhydrin test). The impurity was initially present as a very minor component which could be detected in the infrared spectrum (ν_{max} 1725 cm^{-1}). This was analogous to the impurity observed in the preparation of the propyl compound (144) (see p.77).

Further evidence for the presence of an impurity was gained by noting that the primary amines (204) and (210) both contained ^1H n.m.r. integrals for the 18.1ω9 olefin lower than expected, when compared to the acrylyl olefin proton integral. The amines also possessed smaller ^1H n.m.r. peaks for the protons of the methylenes α- to the primary amine.

One hydrolysis did not afford the primary amine in high yield. (N-(2-Aminoethyl)-N-[2-(3,3-dimethylacrylamido)-ethyl]acetamide (214) was very polar and was isolated in only 13% yield after partitioning between saturated aqueous sodium chloride and 5% 2-propanol/chloroform. It was also less pure than other members of the series.

The compound isolated by the normal dichloromethane work up (19% yield) was not identified, but it possessed a strong absorption at *ca* 1735 cm^{-1} in the infrared spectrum characteristic of the impurity previously noted (p.77).

TABLE IV : Reaction Yields and Purified Yields of the Primary Amines and the Acarnidines.

$Me_2C=CHCONH(CH_2)_xNR(CH_2)_yNHR'$

x	y	R	No.	Yield (R=H) %	No.	Yield (R=C(=NH)NH$_2$) %	
(propyl)	6	12.0	(144)	87*	(145)	82*	37**
3	6	12.0	(154)	100	(155)	90	67
3	6	18.0	(199)	91	(216)	87	60
3	6	18:1ω9	(200)	88	(217)	97	35
3	5	2.0	(201)	88	(218)	77	10
3	5	12.0	(202)	94	(219)	89	40
3	5	18.0	(203)	88	(220)	80	40
3	5	18:1ω9	(204)	86	(221)	89	60
3	4	12.0	(205)	98	(222)	78	45
3	4	18.0	(206)	94	(223)	99	30
3	4	18:1ω9	(207)	98	(224)	84	50
3	2	12.0	(208)	98	(225)	81	10
3	2	18.0	(209)	98	(226)	75	15
3	2	18:1ω9	(210)	98	(227)	77	10
5	5	12.0	(211)	91	(228)	89	15
5	2	12.0	(212)	97	(229)	87	10
2	5	12.0	(213)	98	(230)	94	10
2	2	2.0	(214)	13	(231)	100	5
2	2	12.0	(215)	86	(232)	80	20

* Crude yields ** Purified yields

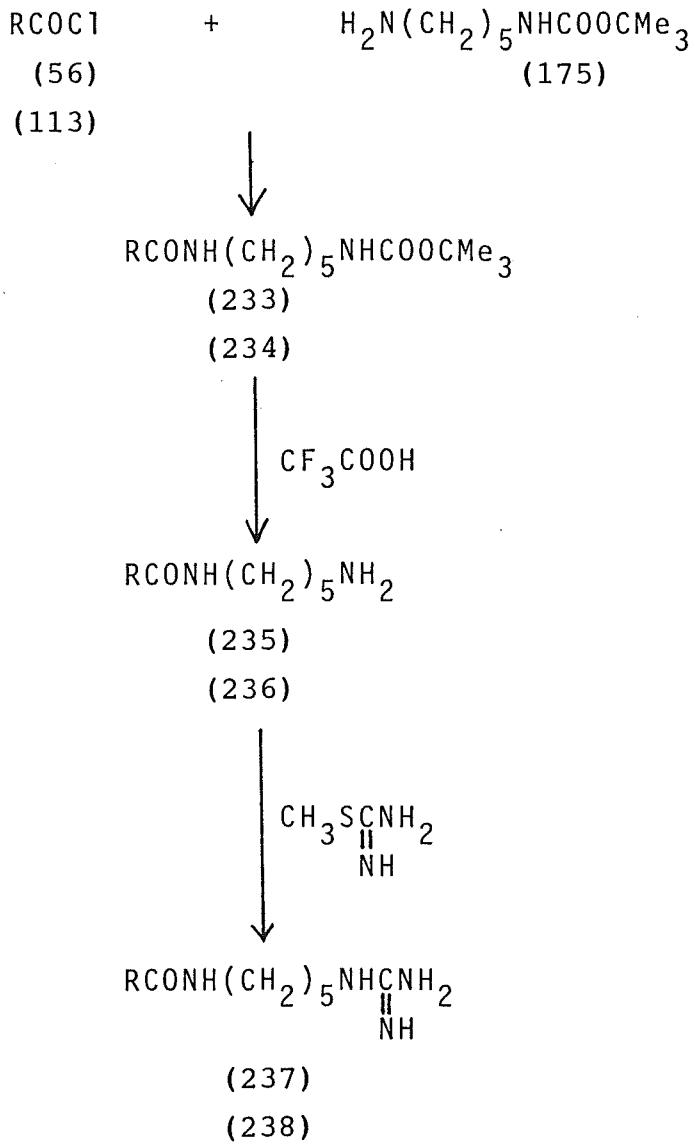
The 2,2-dodecanamide (215) and 3,5-acetamide (201) analogues were more stable.

All of the amines were reacted immediately after preparation with S-methylisothiouronium iodide (119) in ethanol at room temperature, by the method established for the preparation of the acarnidine analogues (145) and (155) (Table IV).

The acarnidine (227) was isolated from a second guanidino compound which was not identified. The acarnidines (224) and (227) still possessed lower 1ω9 olefin ^{1}H n.m.r. integrals but they were consistent with the defined structure in every other respect.

3.8 Polyandrocarpidine Analogues

Two compounds were prepared by acylation of the monoprotected diaminopentane (175). They were to provide an alternative structural class intermediate between the acarnidines (1) and the polyandrocarpidines (37). The appropriate guanidino compounds were prepared according to Scheme XV by the usual methods.



R = - $COCH=CMe_2$ in (233), 98%; (235), 56%; (237), 55%.*

R = - $CO(CH_2)_{10}CH_3$ in (234), 83%; (236), 81%; (238), 45%.

* % corresponds to the appropriate reaction yield after chromatography (when used).

SCHEME XV

3.9 Purification and Analysis of the Acarnidines

The crude 3,6-acarnidine (157) (*vide supra*) was submitted to a variety of purification methods but only gel permeation chromatography on Fractogel PGM 2000 with ethanol eluent provided the pure acarnidine free of material positive to ninhydrin (ν_{max} 1725 cm^{-1}) and less polar compounds (e.g. dodecanoic acid). Gel permeation is an ideal medium for chromatography as it is chemically inert, thus preventing chemisorption of compounds on to its surface.

Factors other than molecular size influenced the purification of the acarnidines. The order of elution for the most part was non polar compounds followed by the acarnidine, in turn followed by the amine. This is contrary to the expected order in which the higher molecular weight acarnidine should be eluted first. In one case the acarnidine (226) eluted last. The elution of the acarnidines was monitored by Sakaguchi and ninhydrin reagents. The amine was visualized as a bright plum red colour with ninhydrin (t.l.c., 5 min at 120°), whereas the acarnidine was visualized only as a very pale violet colour (t.l.c., 15 min at 120°), which rapidly faded, with ninhydrin. Sakaguchi reagent reacted with the guanidino function to form a scarlet colour.

The crude yield of all the acarnidines except for the 2,2-acetyl analogue (231) was greater than 75% (see Table IV). As described earlier, tailing on the column

(ethanol or 2-propanol eluents) meant only small fractions of some of the acarnidines were recovered entirely free of material showing a positive ninhydrin test. Some acarnidines required preparative t.l.c. for the final purification which reduced the yield occasionally to $\leqslant$ 10% (see Table IV).

Other methods of purification were attempted, but failed, including preparative t.l.c. on silica gel (extensive tailing), column chromatography on silica gel, Florisil, octadecylsilane (reverse phase), Sephadex LH-20; ion exchange chromatography on Zeo-Karb 225, Dowex 50W-X8, Amberlyst 15; partitioning (phosphate buffer) and h.p.l.c. (cyanopropylsilane in the normal phase, and octadecyl- and octylsilane reverse phases).

High resolution fast atom bombardment (f.a.b.) mass spectra have been recorded for the acarnidines to unequivocally establish their identities.

Low resolution f.a.b. mass spectra were also recorded for the acarnidines (155),(185),(218), and (225-232), as it was considered to be a very good means of confirming the structural integrity and purity of the acarnidines. If the acyl migration had occurred during the preparation of work up of the primary or secondary amines a "scrambled" ion fragmentation pattern might have been detected from molecular ions of the same molecular weight. Most of the daughter peaks had an intensity of less than 5% of the quasi molecular (MH^+ion) base peak and originated only from the acarnidine type skeleton. The acarnidine (218) contained a minor high molecular weight impurity but the acarnidines (227) and (231), as expected, possessed several unidentifiable impurity peaks.

F.a.b. mass spectrometry is a recent development of secondary ion mass spectrometry[99]. The technique of f.a.b. involves the direct bombardment of a sample by a beam of fast neutral argon atoms causing ejection (sputtering) of the sample (secondary gas phase) ions[100]. The ions are then accelerated, focussed and analysed in the usual manner. Normal secondary ion mass spectrometry uses a high energy charged ion beam (^{252}Cf) which can cause changes in the surface characteristics of the sample. The high energy beam is however, capable of generating detectable molecular ions of very high molecular weight organic compounds (>4000 a.m.u.) whereas the lower energy f.a.b. method is considered more suitable for lower molecular weight compounds ($\leqslant$4000 a.m.u.). The high energy methods are not yet commercially available.

A sample's surface may also be altered by f.a.b. and therefore a means of maintaining a fresh sample surface in the beam to increase the sample lifetime has been developed. A paste of the sample made with glycerol allows the surface to "bleed" under f.a.b., thus continually exposing a fresh surface. The extended lifetime of the sample produces a greater sensitivity which allows accurate mass measurements and identification of structurally significant fragment ions, in contrast to the normal field desorption methods.

Organic salts (e.g. the acarnidines) are readily measured by f.a.b. but neutral organic molecules (e.g. the disubstituted amides) often require the addition of ionic compounds, like sodium chloride so that MNa^+ adduct

ions are formed. Adduct ions are preferentially formed from neutral molecules which increase the peak intensities so that mass measurements can be made.

Normal electron impact and chemical ionization methods are limited as they cannot analyse thermally labile compounds (chemical ionization was barely suitable for the disubstituted amides) nor can they analyse involatile compounds (organic salts or high molecular weight compounds).

^{13}C n.m.r., as mentioned earlier, was an excellent method for fingerprinting the acarnidines. The chemical shift of each unsaturated carbon was unambiguously allocated to the appropriate carbon atom and the presence or absence of any peak was a suitable measure of purity. Characteristic shifts were δ_C118(=$\underline{C}$HCONH), 150($Me_2\underline{C}$=), 157[NH$\underline{C}$(=NH)NH_2], 168(-CH$\underline{C}$ONH), 174 ppm ($CH_2\underline{C}$ON).

In some of the acarnidines, the carbonyl and olefin peaks were multiplets (normally doublets). However, when for example, the 3,6-acarnidine (155) was converted to the pyrimidine (156) in quantitative yield the multiplets collapsed to singlets confirming that all of the peaks belonged to the same compound. This feature was also evident in the ^{13}C n.m.r. spectra of the acarnidine natural products[101]. When the mixture (1a-c) was converted to the pyrimidines all the resonances due to the unsaturated carbons collapsed to singlets. No satisfactory explanation is evident for this, even though further information was sought by repeating the ^{13}C n.m.r. data collection in

pyridine-d_5 and water and in chloroform-d at 0° and 56°.

The n.m.r. solvent, pyridine-d_5, was used to rule out the possibility that the planar guanidino group was interacting with the planar dimethylacrylamido group. Intramolecular processes that could align two planar groups in fixed orientations could have accounted for the appearance of doublet acrylamide peaks. The function of the planar pyridine was to prevent the possibility of this process from occurring. No significant change was observed.

Another solvent, water, was used to detect any effects as a result of a large increase in the polarity of the n.m.r. solvent but no significant changes were observed.

The third approach to determine causes for the peaks and the N-C_α carbon line broadening (*vide infra*) was to record ^{13}C n.m.r. spectra at different temperatures. Changing the temperature of the solution should indicate whether the unusual features were results of temperature dependent inversion processes centred at the nitrogen atoms.

In concert with the ^{13}C n.m.r. data, the low resolution f.a.b. spectra of the acarnidines (155) and (219) did not indicate the presence of impurities.

As mentioned above another aspect of the ^{13}C n.m.r. data was the existence of line broadening for the carbon atoms α- to the nitrogen atoms. This broadening was present in the acarnidine chloride (155) as well as the iodides but was not observed for any of the synthons.

TABLE V : U.V. Absorption Spectra of the Acarnidines and Other Representative Compounds.

$Me_2C{=}CHCONH(CH_2)_xNR(CH_2)_yNHC(=NH)NH_2$

x	y	R	Number	λ_{max} nm (ε)	$\lambda_{inflection}$ nm
(propyl)	6	12.0	(145)	218 (16 000)	208
3	6	12.0	(155)	209 (22 000)	
			(155)	213 (27 000)*	
3	6	18.0	(216)	210 (23 000)	
3	6	18:1ω9	(217)	210 (20 000)	
			(217)	215 (19 000)*	
3	5	2.0	(218)	218 (27 000)	208
3	5	12.0	(219)	217 (26 000)	208
3	5	18.0	(220)	208 (20 000)	
			(220)	216 (16 000)*	
3	4	12.0	(222)	209 (24 000)	
3	4	18.0	(223)	209 (22 000)	
3	4	18:1ω9	(224)	207 (21 000)	
3	2	12.0	(225)	207 (8 000)	
3	2	18.0	(226)	219 (33 000)	207
3	2	18:1ω9	(227)	218 (28 000)	208
5	5	12.0	(228)	216 (32 000)	208
5	2	12.0	(229)	218 (27 000)	207
2	5	12.0	(230)	220 (27 000)	
2	2	2.0	(231)	220 (30 000)	207
2	2	12.0	(232)	219 (31 000)	208
$Me_2C{=}CHCONH(CH_2)_5NHC(=NH)NH_2$			(237)	220 (27 000)	
			(237)	219 (12 000)*	
$CH_3(CH_2)_{10}CONH(CH_2)_5NHC(=NH)NH_2$			(238)	220 (17 000)	
$H_2N(CH_2)_6NHC(=NH)NH_2 \cdot \frac{1}{2}H_2SO_4$			(74)	195 (6 500)	192 (6 500)
$H_2N(CH_2)_6NHC(=NH)NH_2 \cdot HI$			(87)	219 (16 000)	207
$H_2NC(=NH)NH_2 \cdot HI$			(4.HI)	225 (10 000)	195 (9 000)
			(4)	225 (4 400)*	
$Me_2C{=}CHCONH(CH_2)_3OH$			(139)	218 (17 000)	(symmetrical)
$Me_2C{=}CHCONH(CH_2)_3N(CH_2)_5NHCOOCMe_3$			(185)	210 (19 000)	
$CH_3(CH_2)_{10}CO$					

* U.V. spectrum recorded in methanolic potassium hydroxide.

The ultraviolet spectra (Table V) depict two classes of ultraviolet absorptions. The compounds which absorbed at *ca* 208 nm were skewed towards the longer wavelengths whereas those acarnidines which possess a maximum absorption at *ca* 218 nm all possess inflections at *ca* 208 nm. All the maxima of the acarnidines measured in neat methanol are broad.

The compounds that were run in a 1% solution of 2M potassium hydroxide in methanol have slightly different extinction coefficients for λ_{max} but have become sharper and more symmetrical. The λ_{max} for those absorbing at 208 nm shifts to a longer wavelength upon the addition of base.

Some trends can be observed. All of the guanidino compounds that are not acarnidines absorb at *ca* 220 nm including the acrylamide derivative (237). (3-Hydroxypropyl)-3,3-dimethylacrylamide (139) also absorbs at 218 nm but the N,N-disubstituted amide (185) absorbs at 210 nm. The other carbonyl functions within the molecule (185) while not having chromophores (λ_{max}<200 nm) influence the acrylamide absorption causing an absorption shift to a shorter wavelength.

The acarnidines therefore possess properties that encourage absorptions at the differing wavelengths and each one must be considered to be a unique case.

The wavelength absorption shift resulting from the addition of base can be described in terms of a reduction of the polarity of the guanidino group, thus reducing its influence on the acrylamido group. The property that

favours one maximum over the other for the acarnidines recorded in neat methanol cannot be determined at this level of analysis.

No evidence of transacylation to the guanidino group was apparent as absorption maxima for acylguanidines occur at >230 nm[18].

No correlation could be made between the unusual ^{13}C n.m.r. results and the unusual ultraviolet absorption results.

CHAPTER III

CONCLUSION

The synthesis of the acarnidines was approached from a number of different directions. Although many methods failed unexpectedly, several approaches looked promising. What originally appeared to be a simple synthesis was often thwarted by such difficulties as reaction medium polarity and the solubilities of the reagents. The availability of chemicals, their reactivity and work up also presented difficulties.

Twenty-one acarnidines were ultimately prepared *via* Schiff base intermediates. The original target molecule, 2,6-acarnidine (53) was not prepared, as greater interest evolved around the synthesis of the 3,5-acarnidine (219). The approach to the 2,6-acarnidine (53) has been established.

Although acarnidines based on 4-aminobutanol (159) could not be prepared, a successful route to the appropriate acarnidines could be possible. The successful hydrolysis of N-(2,2-dimethoxylethyl)-3,3-dimethylacrylamide(166) suggests that the same method could be applied to N-(4,4-dimethoxybutyl)-3,3-dimethylacrylamide (239) prepared from commercially available aminobutyraldehyde dimethylacetal (240).

Bioassays of the compounds are being undertaken by the Botany Department, University of Canterbury, N.Z., the Upjohn Company, Kalamazoo, U.S.A., and the Cancer Research Institute, Auckland, N.Z.

A consideration important in the future bioassay results evolves around the lack of polyunsaturated fatty acyl analogues. Polyunsaturated fatty acids possess a broad range of biological properties, although their antibiotic function is of greater interest to pharmacologists[121]. The acarnidines (1a-c) isolated from the marine sponge were not separated at any time, therefore the biological activity of the individual compounds was not determined. The activity could be stronger for the unsaturated compounds, (1b) and (1c), by correlation to the polyunsaturated fatty acids.

Polyunsaturated acarnidines analogues will need to be prepared before a full understanding of the biological activity of the acarnidines can be claimed.

EXPERIMENTAL

Infrared spectra were recorded on a Shimadzu IR-27G spectrophotometer; ultraviolet spectra were recorded on a Varian Super Scan 3 spectrophotometer; high resolution electron impact mass spectra were obtained on an AEI MS-902 mass spectrometer and low resolution mass spectra [electron impact (e.i.) or chemical ionization (c.i.)] were obtained on a Hewlett-Packard GCMS 5982A mass spectrometer. Fast atom bombardment (f.a.b.) low and high resolution (h.r.) mass spectra were obtained on a Varian MAT 731 mass spectrometer in the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois, Urbana, USA, supported in part by a grant from the National Institute of General Medical Sciences (GM 27029).

^{1}H n.m.r. spectra were recorded on a Varian T60, or, on a Varian EM 360A, or, along with ^{13}C n.m.r. spectra on a Varian CFT-20 spectrometer. The n.m.r. samples were prepared in $CDCl_3$ solutions and measured in parts per million from $SiMe_4$ as an internal standard, unless otherwise stated.

Melting points were recorded in open capillaries and are uncorrected; and micro analyses were undertaken by the Chemistry Department, Univeristy of Otago, Dunedin, N.Z.

High performance liquid chromatography (h.p.l.c.) was performed on a Varian Model 5020 liquid chromatograph fitted with a Varian UV-50 variable wavelength detector. Where mentioned, some h.p.l.c. was performed on a Waters ALC-100 liquid chromatograph fitted with a refractive index detector.

The technical grade solvents were purified according to the methods described in "The Chemist's Companion"[102], except for ethanol. Each litre of ethanol was refluxed for 1 h with 7 g of sodium and 27.5 g diethylphthalate before distillation. The alcohols when necessary were stored over 3 Å molecular sieves (Sigma) and other solvents over 4 Å molecular sieves.

"Pet ether" refers to petroleum ether distilled between 50° and 70°, whereas "ether" refers to diethyl ether distilled and stored over sodium wire.

Triethylamine (BDH) was stood over sodium hydroxide and used without distillation, whereas pyridine was purified before storage over sodium hydroxide.

Acetonitrile (BDH) was stood over 4 Å molecular sieves and used without distillation.

In the following account of experimental preparations and reactions "work up in the usual manner" (or "work up") will refer either to the method previously outlined for a similar reaction, or to the following more general procedure: partitioning with chloroform (or dichloromethane or 10% 2-propanol/chloroform); then aqueous wash of the organic solution with 1-5% hydrochloric acid followed by 5% base (sodium hydroxide, carbonate or bicarbonate); wash with brine; drying of the extract over anhydrous sodium sulphate (or equal portions of sodium sulphate and potassium carbonate for free amines); separation from the drying agent by filtration; and removal of the solvent in a Büchi rotary evaporator to give the crude organic product.

"Dried and evaporated" relates to the stages of work up described above, which includes the wash with brine and subsequent steps.

Ninhydrin reagent was prepared according to the method in "The Chemist's Companion"[102] and the Sakaguchi reagent was prepared according to the method described in the "Handbook of Chromatography"[103]. Both reagents were delivered by atomizers to thin layer chromatography (t.l.c.) plates or to paper.

SECTION 1 : ATTEMPTED APPROACHES TO THE ACARNIDINES

Diphenylphosphinyl chloride (54)

Diphenylphosphinyl chloride (54) was prepared from chlorodiphenylphosphine (59) (Aldrich), according to the method of Haake *et al*[43], (64%), b.p. 164-166° (1 mm) [lit. b.p. 199-201° (8 mm)]. (Found: M^+, 236.0101. $C_{12}H_{10}ClOP$ requires 236.0158).

Ethylenebis(diphenylphosphinamide) (58)

To a solution of 519 mg (8.64 mmol) of 1,2-diaminoethane in 8 ml of pyridine and 10 ml of benzene was slowly added 4.28 g (18.1 mmol) of diphenylphosphinyl chloride (54) in 4 ml of benzene. The mixture was heated at reflux for 2 h. A saturated solution of sodium carbonate (20 ml) was shaken with the reaction mixture and the benzene solution was isolated. The aqueous solution was washed with ethyl acetate and the combined organic extracts were backwashed with water, dried and evaporated to afford the phosphinamide (58) as a white amorphous solid (3.30 g, 83%), m.p. (methanol/acetone) 233-234°. ν_{max} 3200, 1170, 1100, 750, 730, 570 cm^{-1}. ^1H n.m.r. $\delta_H(CD_3OD)$ 3.1, m, 4H; 6.8 - 7.5, m, 20H. ^{13}C n.m.r. $\delta_C(CD_3OD)$ 43.3, 43.6, 129.4, 130.1, 132.8, 133.3.

N-(Butyl)ethylenebis(diphenylphosphinamide) (60)

To 100 ml of tetrahydrofuran, was added 670 mg (1.46 mmol) of the phosphinamide (58) and 200 mg (1.46 mmol) of bromobutane, with swirling, followed by sodium hydride (54 mg, 2.2 mmol)[21]. The flask was set up and heated at reflux. The phosphinamide (58) took 0.5 h to dissolve and after 3 h, ethyl acetate was added to destroy any sodium hydroxide still present. The solution was evaporated to near dryness, washed with 10 ml of water and extracted with ethyl acetate (3 x 10 ml), dried over potassium carbonate and evaporated to produce a gum (674 mg, 90%) which would not solidify after attempted crystallisation from 2-propanol, acetone, ethyl acetate or mixtures of these with ether or pentane. Only one compound was apparent by t.l.c. ν_{max} 3200, 2950, 1470, 1170, 1100, 750, 730, 570 cm^{-1}. ^{1}H n.m.r. $\delta_H(CD_3OD)$ 0.8, bt, 3H; 1.4, m, 4H; 2.7 - 3.4, m, 6H; 7.2 - 8.1, m, 20 H. ^{13}C n.m.r. $\delta_C(CD_3OD)$ 13.8; 20.7, 31.8, 39.7, 43.2, 43.5, 129.2, 129.9, 132.6, 133.1, 133.4.

N-(Acetyl)-N'-(butyl)ethylenebis(diphenylphosphinamide) (61)

To a stirred solution of 743 mg (1.44 mmol) of the phosphinamide (60) in 10 ml of tetrahydrofuran, was slowly added 113 mg (144 mmol) of acetyl chloride followed by 81 mg (2.2 mmol) of sodium hydride. The reaction flask was set up for reflux with a drying tube and heated. After 3.5 h, a little ethyl acetate was added and most of the solvent was removed *in vacuo*. Sodium bicarbonate (5%) solution (10 ml) was added then extracted with ethyl acetate (3 x 10 ml), dried and evaporated to an oil (748 mg, 58%).

ν_{max} 2900, 1650, 1170, 1100, 750, 730 cm^{-1}. ^1H n.m.r. $\delta_H(CD_3OD)$ 0.85, t, 3H; 1.2, m, 4H; 1.97, s, 3H; 2.7 - 3.4, m, 6H; 7.1 - 8.1, m, 20 H. ^{13}C n.m.r. $\delta_C(CD_3OD)$ 13.8, 20.7, 22.6, 31.6, 38.7, 45.7, 46.7, 129.4, 130.0, 132.5, 132.9, 133.4. Mass spectrum; M^+ not observed. Found: 286.1362. $[(C_5H_5)_2PON(CH_2)_3CH_3]^+$ requires 286.1361. Found: 201.0460. $[(C_6H_5)_2PO]^+$ requires 20.0461.

N-[(Butylamino)ethyl]acetamide (62)

The phosphinamide (61) (400 mg, 0.70 mmol) was dissolved in 5 ml of 2M HCl in dioxan/water (2:1) and stirred 2.5 h according to the method of Ramage *et al.*[21]. The solution was evaporated at room temperature, extracted with 2-butanol, then made alkaline with aqueous ammonia (0.88) and extracted again with 2-butanol, dried and evaporated. The amide (62) was isolated as the hydrochloride from the acidic fraction (96 mg, 65%). ν_{max} 3300, 2950, 2300, 1660, 1570 cm^{-1}. ^1H n.m.r. δ_H0.85, bt, 3H; 1.1-1.5, m, 4H; 1.95, s, 3H; 2.7-3.4, m, 6 H. ^{13}C n.m.r. δ_C13.6, 20.0, 22.9, 29.7, 36.5, 47.8, 47.9, 171.4.

Attempted Preparation of N-(Methyl)ethylenebis(diphenylphosphinamide) (63)

(i) Attempted preparation of the N-methyl derivative (63) was by the same method as for the preparation of the N-butyl product (60) except iodomethane was the alkyl halide; only starting material was isolated (m.p., mixed m.p., ^1H n.m.r.).

(ii) By the above method, except 2 ml of hexamethylphosphoramide (HMPA) was added. No reaction occurred (m.p., ^1H n.m.r.).

(iii) A two phase system of 15 ml of 50% aqueous sodium hydroxide and 15 ml of toluene was used. Iodomethane (200 mg, 1.41 mmol) was added to 400 mg (0.87 mmol) of the phosphinamide (58) and tetrabutylammonium hydroxide (36 mg) and stirred over night at room temperature[22]. The mixture was extracted with 2-butanol, which was dried and evaporated. Only starting material was isolated (m.p. ^{1}H n.m.r.)

N-(Ethyl)ethylenebis(diphenylphosphinamide) (64)

Iodoethane (5.69 g, 36.5 mmol) was slowly added to a suspension of 11.16 g (24.3 mmol) of the phosphinamide (58) and 0.58 g (24.3 mmol) of sodium hydride heated at reflux in tetrahydrofuran. The suspension dissolved within 45 min but heating was maintained for 2 h, after which a little ethyl acetate was added. The solvent was evaporated then 75 ml of water was added and worked up with 15% 2-propanol in chloroform (3 x 50 ml) to afford a viscous oil. Unreacted starting material was removed by crystallization from chloroform. The sample was not purified further as h.p.l.c. (Waters ODS, 30% water/methanol) indicated a purity of about 88% (5.6 g, 60%). ν_{max} 3200, 2950, 1470 1170 1100 cm^{-1}. ^{1}H n.m.r. δ_H1.0, bt, 3H; 3.2, m, 6H; 4.95, broad, 1H; 7.2-8.1, m, 20H, ^{13}C n.m.r. δ_C13.6, 41.0, 46.4, 46.9, 128.1, 128.8, 131.7, 132.2.

3,3-Dimethylacryloyl chloride (56)

3,3-Dimethylacrylic acid (Aldrich) and thionyl chloride (1.5 mole equivalents) were heated at reflux for 2 h. The

acyl chloride (56), isolated and purified twice by distillation, was stored in the dark under nitrogen (40%). B.p. 145-150° (lit. b.p. 145-150°)[104]. ^{1}H n.m.r. 1.98, s, 3H; 2.08, s, 3H; 6.0, s, 1H.

Attempted Preparation of N-Ethyl-N'-(3,3-dimethylacryloyl-ethylenebis(diphenylphosphinamide) (65)

A tetrahydrofuran solution of 167 mg (1.4 mmol) of 3,3-dimethylacryloyl chloride (56) was added to a solution of 417 mg (0.9 mmol) of the amide (64) and sodium hydride (67 mg, 2.8 mmol) heated at reflux in 10 ml of tetrahydrofuran. No reaction was observed by t.l.c. After 2 h, one half of the reaction mixture was worked up in the manner of compound (61) and, after 2 days, the remainder was also worked up to recover only the starting compound (64) in each case (i.r. and n.m.r.).

Octyl *p*-toluenesulphonate (67)

At 0°, 4.4 g (23 mmol) of *p*-toluenesulphonyl chloride was added dropwise to a stirred solution of 3 g (23 mmol) of octanol in 50 ml of pyridine[105]. The mixture was stirred overnight at 25°. Ice cold water (100 ml) was added and work up with ether afforded 4.33 g of an oil (64%). ν_{max} 2900, 1920, 1345, 1180, 1170, cm^{-1}. ^{1}H n.m.r. δ_H 0.9, t, 3H; 1.25, s, 10H; 1.3-2.0, m (broad), 4H; 2.44, s, 3H; 4.0, t, 2H; 7.3, d, 2H; 7.8, d, 2H. ^{13}C n.m.r. δ_C14.1, 21.6, 22.6, 25.4, 26.9, 28.9, 29.1, 31.8, 45.1, 127.9, 129.8, 144.6, 149.9.

Attempted Preparation of N-Octylguanidinium *p*-toluenesulphonate (68)

This reaction followed the procedure devised by Munro[30]. To 20 ml of *tert*-butanol was added 169 mg (7.0 mmol) of sodium hydride followed by 674 mg (3.7 mmol) of guanidinium carbonate (Fluka). The suspension was heated at reflux with stirring for 0.5 h, then sodium carbonate was filtered from the hot solution and the filtrate was added to the sulphonate (67) in 5 ml of *tert*-butanol. The mixture was heated at reflux overnight, then evaporated. Water (10 ml) was added and work up with ether (2 x 10 ml) afforded a quantitative amount of octanol (n.m.r.). Acetone was added to the aqueous phase until crystals of guanidinium *p*-toluenesulphonate (69) began to separate, m.p. (5% acetane/water) 219-220°(dec) [mixed m.p. 219°(dec)]. ν_{max} 3350, 1680, 1180 cm^{-1}. ^1H n.m.r. δ_H 2.25, s, 3H; 7.05, s, 6H; 7.15, d, 2H; 7.56, d, 2H.

Guanidinium *p*-toluenesulphonate (69)

A solution of 2.0 g (11.0 mmol) of guanidinium carbonate in 20 ml of water was added slowly with swirling to 4.22 g (22.2 mmol) of *p*-toluenesulphonic acid (Aldrich) dissolved in 20 ml of water. Effervescence occurred and crystals rapidly settled. The crystals of the sulphonate (69) were isolated by filtration and air dried, m.p. 219-220° (dec.) and m.p. (picrate) 332° [lit. m.p. (picrate) 333°][104].

Attempted Preparation of N-(2-Aminoethyl)-3,3-dimethylacrylamide (71)

To a stirred solution of 3.00 g (50 mmol) of 1,2-diaminoethane and 5.09 g (100 mmol) of triethylamine in 50 ml of dichloromethane at 0°, was added 5.92 g (50 mmol) of dimethylacryloyl chloride (56) in 10 ml of dichloromethane at the rate of one drop per second. The solution was stirred overnight at room temperature, then washed with 50 ml of 5% aqueous sodium hydroxide, dried and evaporated. The residue was identified as the 1,2-bis(amide) (71) (quantitative yield), m.p. 190-191° (Found: M^+, 224.1511. $C_{12}H_{20}N_2O_2$ requires M^+ 224.1524). ν_{max} 3350, 2950, 1675, 1630 cm^{-1} ^1H n.m.r. δ_H (Me_2SO-d_6) 1.83, s, 6H; 2.15, s, 6H; 3.24, m, 8H; 5.60, s, 2H; 6.38, bt, 2H(exchanged by D_2O). ^{13}C n.m.r. δ_C(Me_2SO-d_6)18.4, 25.9, 37.7, 118.2, 147.5, 165.3.

N-(2-Aminioethyl)-3,3-dimethylacrylamide chloride (71.HCl)

A solution of 3.94 g (33.3 mmol) of 3,3-dimethylacryloyl chloride (56) dissolved in 15 ml of dichloromethane was added dropwise to a stirred solution of 2.00 g (33.8 mmol) of 1,2-diaminoethane in 50 ml of dichloromethane at 0°. When all of the acyl chloride (56) was added, the solution was allowed to warm to room temperature and stirring was continued a further 3 h. The residue was recovered by filtration and recrystallized from methanol to give the aminium chloride (71.HCl) (5.38 g, 91%), m.p. 190-192° (dec). ν_{max} 3300, 2700, 2050, 1670, 1630, 1550, 1290 cm^{-1}. ^1H n.m.r. δ_H (Me_2SO-d_6) 1.80, s, 3H; 2.08, s,

3H; 3.13, t, 4H; 5.61, s, 1H; 4.0-6.6, broad, 3H (exchanged by D_2O); 7.80, s, 1H (exchanged by D_2O). ^{13}C n.m.r. $\delta_C(Me_2SO\text{-}d_6)$ 20.1, 28.3, 39.0, 39.8, 120.7, 149.9, 167.8.

Attempted Preparation of N-[2-(Butylamino)ethyl]-3,3-dimethylacrylamide (73)

A solution of 388 mg (2.83 mmol) of bromobutane in 20 ml of methanol was added dropwise to a stirred suspension of 510 mg (2.86 mmol) of the aminium chloride (71.HCl) and 481 mg (5.72 mmol) of sodium bicarbonate in 20 ml of methanol. The form of the suspension changed over 4 h, by which time no starting amine (71) remained, according to t.l.c. The methanol was removed *in vacuo*, water (10 ml) was added and worked up with 10% 2-propanol in chloroform to yield the 1,2-bis(amide) (72) m.p. 191-192°, mixed m.p. with the previously prepared 1,2-bis(amide) (71) 191-192°. ν_{max} 330, 1675, 1630 1550 cm^{-1}. ^1H n.m.r. δ_H 1.83, s, 6H; 2.15, s, 6H; 3.42, m, 8H; 5.60, s, 2H; 6.3, bs, 2H.

Other attempts to prepare the amine (73) were by:

(i) ethyl acetate as solvent (bis product),

(ii) pyridine as base and solvent (bis product),

(iii) two mole equivalents of silver nitrate in distilled water (no reaction),

(iv) silver nitrate, buffered to pH 9.9 with bicarbonate/carbonate buffer (no reaction), and

(v) two phase Schotten-Baumann method without and with heating (80°) (no reaction).

S-Methylisothiouronium sulphate (75)

Prepared according to the method of Shildneck and Windus[106] (81%), m.p. 244° (dec.) [lit. m.p. 244° (dec)][106]. ^{13}C n.m.r. (H_2O) 13.9, 174.0.

Aminoguanidinium sulphate (77)

Prepared according to the method of Smith and Anzelmi[107], (95%), m.p. 206-208° (dec.)(lit. m.p. 206°).

1-Guanyl-3,5-dimethylpyrazolium sulphate (76)

The pyrazole (76) was prepared according to Bannard's synthesis of the pyrazolium nitrate.[32]

In portions, 22.0 g (89.4 mmol) of the amine (77) was added within 0.75 h to a solution of 17.94 g (179 mmol) of 2,4-pentanedione in 100 ml of 50% aqueous ethanol heated at reflux. The resultant mixture was heated for a further 2.25 h. The mixture was evaporated to a viscous oil which was triturated with ether until a brittle, deliquescent gum remained. The anhydrous pyrazolium sulphate (76) was recovered after vacuum desiccation (0.1 mm) for 48 h (22 g; 65%), m.p. (picrate) 205-208° (lit. m.p. 206-208.5°)[32]. ^{13}C n.m.r. $\delta_C(H_2O)$ 12.9, 13.5, 113.8, 145.1, 154.3, 156.7.

N-(6-Aminohexyl)guanidinium sulphate (74)

(i) To a stirred solution of 3.22 g (27.8 mmol) of 1,6-diaminohexane (Koch-Light) in 50 ml of ethanol was added 3.45 g (9.2 mmol) of the pyrazole (76). The mixture was heated at reflux for 2 h then

evaporated to a gum. The product was purified by ether extraction in a Soxhlet apparatus. The residue was dissolved in water and crystallized upon the addition of acetone. Two distinct crystalline products were obtained. The first was identified as N-(6-aminohexyl)guanidine (74) (382 mg, 10%), m.p. 298-299° (dec) ν_{max} 3350-2250, 2100, 1680, 1630, 1550, 1070 cm^{-1}. ^{13}C n.m.r. $\delta_C(H_2O)$ 26.1, 26.3, 27.7, 28.7, 40.9, 42.3, 157.8.

The second and major product (2.85 g, 75%) was identified as 1,6-diguanidinohexane (78), m.p. > 330°. ν_{max} 3350-2250, 1680, 1630, 1070, 725 cm^{-1}. ^{13}C n.m.r. δ_C (H_2O) 26.2, 28.6, 42.1, 157.8.

(ii) The reaction with the pyrazolium sulphate (76) was repeated in the absence of solvent and heated over steam (2 h), but only the bis product (78) was isolated.

(iii) To a solution of 23.45 g (201.8 mmol) of 1,6-diaminohexane, heated at reflux in 150 ml of ethanol, was added 18.72 g (67.3 mmol) of the thiourea (75) in small portions within 0.75 h. The solution was heated for 2 h before cooling. The residue was collected by filtration, then purified by selective crystallization after dissolving the bulk of the solid in a minimum of water at room temperature. The insoluble material was removed by filtration and the 6-aminohexylguanidine (74) was recrystallized by the addition of ethanol (16.4 g, 50%), m.p. 298-299° (dec), mixed m.p. with the guanidine (74)

prepared from the pyrazole: 298-299° (dec).

$\lambda_{max}(H_2O)$ 195 nm (ε 6 500).

(iv) Reaction (iii) was repeated in water heated over steam for 4 h. 6-aminohexylguanidine was isolated by crystalization from ethanol/water in 20% yield (mg, mixed up).

Chloroacetamide (80)

Dry ammonia was bubbled into 28.4 g (0.252 mmol) of ice-cold and vigorously stirred chloroacetyl chloride (Koch-Light) in 30 ml of benzene[108]. After 20 min the voluminous precipitate was removed by filtration and more ammonia was bubbled through the solution (repeated twice). The combined precipitates and the benzene solution were taken up in water (100 ml) and the benzene was removed under a stream of nitrogen. The chloroacetamide (80) crystallized from the aqueous solution after standing overnight (13.4 g, 57%), m.p. 115-116° (lit. m.p. 119°)[108]. ν_{max} 3400, 3200, 1630, 1610, 1230, 1090, 770 cm^{-1}. ^1H n.m.r. δ_H (Me_2SO-d_6) 4.00, s, 2H; 7.4, bs, 2H (exchanged by D_2O).

Chloroacetamide (80) was also prepared from chloroacetyl chloride and ammonium acetate[109], but with only limited success.

Chloroacetonitrile (79)

Dry chloroacetamide (78) (4.00 g, 42.8 mmol) and phosphorus pentoxide (7.29 g, 51.4 mmol) were mixed in a pear-shaped flask and set up for distillation through a

Vigreux column over a gentle flame[47]. The fraction collected between 115 - 130° was added to fresh phosphorus pentoxide and redistilled to give pure nitrile (79) which was stored under nitrogen at 4° (2.58 g, 80%), b.p. ≃ 122 - 124° (lit. b.p. 123-124°)[110] ν_{max} 3040, 2950, 2260, 1425, 930, 745 cm^{-1}. ^1H n.m.r. δ_H4.6. Mass spectrum m/z 75(100%), 48(85), 40(40).

Chloroacetonitrile (78) was also prepared according to the method of Reisner and Horning [110] but with less success. Commercial chloroacetonitrile (79) (Aldrich) was subsequently used, when it became available.

2-(Cyanomethylamino)ethylbenzene (82)

2-Aminioethylbenzene chloride (81) (940 mg, 5.96 mmol) and sodium carbonate (1.26g, 11.9 mmol) were suspended with stirring in 10 ml of benzene[47]. Chloroacetonitrile (79) (450 mg, 5.96 mmol) was added and the mixture heated at reflux for 2 h. Sodium chloride was removed by filtration and the solvent removed *in vacuo*. 2-(Cyanomethylamino)-ethylbenzene (82) was isolated by column chromatography on silica gel (Grace 924) with ether as eluent. (529 mg, 56%) (Found: M^+, 160.1000. $C_{10}H_{12}N_2$ requires 160.1000). ν_{max} 3350, 2900, 2250, 1600, 1500 cm^{-1}. ^1H n.m.r. δ_H 1.35, s, 1H (exchanged by D_2O); 2.80, t, 4H; 3.40, s, 2H; 7.25, s, 5H. ^{13}C n.m.r. δ_C 35.7, 37.1, 49.7, 117.8, 126.4, 128.6, 128.7, 139.1. Mass spectrum m/z 160(36%), 133(34), 132(41), 91(67).

This reaction was repeated in ethanol with sodium bicarbonate, and in pyridine as solvent and base. Both reactions were stirred overnight at 25°. The yield of the cyanomethylamine (82) was similar to the original method in each case.

Attempted Preparation of N-[6 - (Cyanomethylamino) hexyl]-guanidinium sulphate (83)

Chloroacetonitrile (79) (500 mg, 6.6 mmol) was added slowly to a stirred solution of 2.74g(6.62 mmol) of amine (74) dissolved in 30 ml of water. The reaction was monitored by t.l.c. but no reaction was observed. The solution was evaporated to dryness at room temperature to give unreacted amine (74)., m.p. 298-299° (dec), i.r. and n.m.r.

The reaction was repeated in (i) dry dimethylformamide and (ii) water, with the slow addition of one mole equivalent of sodium bicarbonate, without success.

Sodium tetraphenylborate (85)

This compound was prepared according to the method of Khol'tsanfel' and Rickhter[48]. ^{13}C n.m.r. (ethanol) δ 122.1, 125.8, 126.1, 137.0.

N-(6-Aminohexyl)guanidinium tetraphenylborate (84)

A solution of 2.08 g (6.1 mmol) of sodium tetraphenylborate (85) dissolved in 5 ml of water was added to a stirred solution of 1.26 g (3.04 mmol) of aminohexylguanidine (74) dissolved in 5 ml of water. A white flocculent precipitate of the borate (84) immediately formed. The precipitate was collected by filtration and washed with distilled water (2.31 g, 80%), m.p. 149-150°. ν_{max} 3350, 3200, 2950, 2730, 2380, 1660, 1645, 745, 715, 610 cm^{-1}.

Attempted Preparation of N-[6-(Cyanomethylamino)hexyl]-guanidinium tetraphenylborate (86)

To 1.5 g (3.14 mmol) of the amine (84) in 20 ml of tetrahydrofuran was slowly added 237 mg (3.14 mmol) of chloroacetonitrile (79) dissolved in 15 ml of tetrahydrofuran. During the addition of chloroacetonitrile (79) 333 mg (3.14 mmol) of sodium carbonate was added in small portions. The mixture was stirred at room temperature and the reaction followed by t.l.c. No reaction was observed after 4 h, but the reaction was still worked up by evaporation of the tetrahydrofuran and extracted by chloroform to give the unreached amine (84).

The reaction was repeated:

(i) as is, overnight;

(ii) as is, but heated at reflux for 3 h;

(iii) substituting acetonitrile for tetrahydrofuran as solvent;

(iv) substituting sodium bicarbonate for sodium carbonate; and

(v) substituting pyridine for base and solvent.

No nitrile absorbance was detected by i.r., nor a cyanomethyl-amino methylene detected by n.m.r. in any method.

N-(6-Aminohexyl)guanidinium iodide (87)

The sulphate (74) dissolved in water was converted to the iodide (87) by passage through an Amberlite IRA-400(I^-) ion exchange column conditioned with 1 M (15%) sodium iodide (4 ml/ml of resin) and by water (3 ml/ml of resin) until the eluate was neutral to silver nitrate. The

iodide (87), elution monitored by silver nitrate, barium chloride and Sakaguchi reagent, was isolated as a deliquescent solid (0.60 g, 96%). $\lambda_{max}(H_2O)$ 217 nm (ε 16 000) ^{13}C n.m.r. δ 26.0, 26.1, 27.4, 28.5, 40.3, 42.0, 157.3.

Attempted Preparation of N-[6-(Cyanomethylamino)hexyl]-guanidinium iodide (88)

The method followed was that of the attempted preparation of the tetraphenylborate (86) but with methanol as the solvent. There was no reaction (i.r., n.m.r.).

Potassium phthalimide (89)

This compound was prepared according to the method of Salzburg and Supniewski[50].

N-(2-Bromoethyl)phthalimide (90)

This compound was prepared according to the method of Salzberg and Supniewski[50], m.p. 81-82° (lit. m.p. 82-83°).

Attempted Preparation of N-[2-(Butylamino)ethyl]phthalimide (91)

To 400 mg (1.58 mmol) of the phthalimide (90) in 30 ml of ethanol was added 144 mg (1.66 mmol) of aminobutane and the mixture was then heated at reflux. Sodium carbonate (176 mg, 1.5 mmol) was added in portions over 1 h and the mixture heated for a further 2 h. The ethanol was removed by evaporation *in vacuo* and the residue was worked up with chloroform to afford an oil (230 mg). The aqueous extract was made alkaline with 10% aqueous sodium hydroxide and

and extracted with ether, dried and evaporated to an oil (150 mg). In both fractions a mixture was detected by t.l.c. and n.m.r. The desired product was not apparent as a significant component of either fraction.

Attempted Preparation of N-[6-[(2-Phthalimidoethyl)amino]-hexyl]guanidinium tetraphenylborate (92)

To 247 mg (0.97 mmol) of the phthalimide (90) in 10 ml of ethanol was added 463 mg (0.97 mmol) of the amine (84) in 10 ml of ethanol. The mixture was heated at reflux and 0.97 mmol of sodium carbonate was added in portions over 1 h. The mixture was monitored by t.l.c., however no reaction was observed. No reaction was observed after 5 h of heating followed by 60 h at room temperature.

Attempted Preparation of N-[6-(Diphenylphosphinamido)hexyl]-guanidinium tetraphenylborate (101)

To a stirred solution of 2.00 g (4.2 mmol) of amino-hexylguanidine (84) in 30 ml of pyridine over ice was added dropwise 0.99 g (4.2 mmol) of diphenylphospinyl chloride (54). The solution was stirred overnight at room temperature after which 60 ml of water was added to precipitate the borate. The precipitate was recrystallized from methanol to give a product that was not visualized by ninhydrin nor Sakaguchi reagents (1.77 g). m.p. 207-208° (dec.). ^{1}H n.m.r. $\delta_H(Me_2SO\text{-}d_6)$ 7.1, s.

Isoborneol (95)

To 100 g (0.51 mmol) of isobornyl acetate in 310 ml of ethanol was added 50 g of potassium hydroxide dissolved in

100 ml of water. The solution was heated at reflux for 1 h, then poured into 1.25 l of cold water. The isoborneol (95) solidified and was recovered by filtration and air dried (78.0 g, 99%), m.p. 204-206° [lit. m.p. 212° (sealed tube)][111]. ^{1}H n.m.r. δ_H 0.85, s, 3H; 0.92, s, 3H; 1.05, s, 3H; 1.5-1.9, m, 9H (1H exchanged by D_2O); 3.6, t, 1H. ^{13}C n.m.r. δ_C11.3,20.1, 20.5, 27.3, 34.0, 40.4, 45.2, 46.3, 48.9, 79.9.

Phosgene (93)

The batchwise preparation of this compound was based on the method of Vogel[52]. Carbon tetrachloride (479 g, 3.11 mol) was dripped into 203 g of a 3:1 mixture of 98% sulphuric acid and 30% fuming sulphuric acid and 2% (w/w) Kieselguhr heated to 125°. The mixture was mechanically stirred. The phosgene (93) was collected by three methods. Firstly, by entrainment in toluene, secondly by entrainment in ether and thirdly, by liquefaction at -70°. To prevent an explosive expansion of the hydrogen chloride in the third method, the cooling bath was carefully warmed by dropwise addition of acetone over several hours. Dry ice in carbon tetrachloride and salt-ice traps were not adequate as only small quantities of phosgene were collected by these traps.

A colour test for the detection of phosgene was prepared by dipping filter paper into an alcoholic solution containing 10% of a mixture of equal parts of *p*-dimethylamino-benzaldehyde and colourless diphenylamine, then dried.[112]

Benzyl chloroformate (94)

This compound was prepared according to the method of Carter, Frank and Johnston[53]. The solution was evaporated to a mobile oil (95 g, 90%). ν_{max} 1775^{-1} cm.

Isobornyl chloroformate (96)

This compound was prepared according to the method of Fujino et al[39]. Unreacted isoborneol (95) was removed by filtration. The chloroformate was isolated as a mobile oil (80 g, 84%). ν_{max} 1775^{-1} cm. ^{13}C n.m.r. δ_C 11.2, 19.7, 20.5, 26.8, 33.4, 38.3, 45.0, 47.0, 49.8, 90.0, 149.9.

The chloroformate (96) was stored under nitrogen at 4°, however hydrolysis, elimination and rearrangement products rapidly formed. ^{13}C n.m.r. δ_C 68.1, 79.8, 99.0, 125.3, 128.2, 129.0[113]. Before subsequent use of the chloroformate (96), volatile compounds were removed under vacuum (0.5 mm) and isoborneol (95), formed by hydrolysis, was removed by filtration.

4,6-Dimethyl-2-thiopyrimidinium chloride (98)

This compound was prepared batchwise according to the method of Hunt *et al.*[114], (919g,87%).

(4,6-Dimethylpyrimid-2-ylthio)carbonyl chloride (100)

This compound was prepared according to the method of Nagasawa *et al.*[54], except that 2 mole equivalents of sodium hydroxide were reacted with each mole of the chloride (98). The precipitate of the sodium salt (99) was recovered by filtration and dried at 120° for 24 h to obtain a mixture of the thiolate (99) and inorganic salts. Heating initially

melted the salt (99) and the skin that formed needed to be broken to enhance the drying rate. Prolonged drying coloured the salt (99). The salt baked to a very hard mass which was subsequently crushed to a fine powder. The yield of the chloroformate (100) varied from 9 - 65%. Also the chloroformate (100) was unstable, a yellow precipitate formed after 5 min at -10°. ^{1}H n.m.r. δ_H2.48, s, 6H; 7.04, s, 1H.

tert-Butyl 4,6-dimethylpyrimidinyl-2-thiol carbonate (97)

This compound was prepared according to the method of Nagasawa *et al*[54], (39-80 %), m.p. 48-49° (lit. m.p. 50-51°) ^{1}H n.m.r. δ1.45, s, 9H; 2.43, s, 6H; 6.92, s, 1H.

Attempted Preparation of N-[6-(*tert*-Butyloxycarbonylamino)-hexyl]guanidine (102)

To a stirred solution of 433 mg (1.02 mmol) of aminohexylguanidine (74) in 50 ml of water was added in small alternate portions, 192 mg (2.29 mmol) of sodium bicarbonate in 3 ml of water and 500 mg (2.08 mmol) of the thioester (97) in 7 ml of dioxan. After 6 h, 10 ml of water was added and extracted twice with ethyl acetate. According to t.l.c., no reaction had occurred beyond suspected hydrolysis of the thioester (97).

N-[6-(Benzyloxycarbonylamino)hexyl]guanidine (103)

To a stirred, ice cold solution of 1.50 g (4.8 mmol) of aminohexylguanidine (74) and 1.21 g (14.4 mmol) of sodium bicarbonate, was slowly added 1.89 g (11.1 mmol) of

benzyl chloroformate (94). The solution was stirred for 1 h and warmed to room temperature when all the chloroformate had been added. The aqueous solution was extracted with chloroform (3 x 15 ml) and worked up to afford 1.53 g of a viscous oil. T.l.c. in methanol/(0.88) ammonia (4:1) and butanol/pyridine/acetic acid/water (4:1:1:2) revealed the presence of two compounds of higher R_f than the amine (74). The more polar of the two compounds was positive to the Sakaguchi test.

The oil was taken up in 20 ml of 0.1 M formic acid then extracted with dichloromethane (3 x 10 ml) and worked up. The aqueous phase, having retained the positive Sakaguchi test material, was evaporated to dryness at room temperature. Water (5 ml) was added twice more and evaporated to ensure the complete removal of any residual formic acid to finally produce a colourless oil (84 mg, 48% of the extract) of the benzyl carbamate (103). ν_{max} 3350, 3170, 2950, 1700, 1670 (v. broad) 1100 cm^{-1}. ^1H n.m.r. δ_H1.30, bs, 8H; 3.1, bs, 4H; 5.00, s, 2H; 5.80, bs, 1H (exchanged by D_2O); 7.21, s, 5H; 6.5-8.0, broad, 5H (exchanged by D_2O). ^{13}C n.m.r. δ_C26.2, 28.6, 29.6, 41.3, 42.0, 67.6, 128.2, 129.6, 140, 157.

N-[(6-Benzyloxycarbonylamino)hexyl]-N,N'-bis(isobornyloxycarbonyl)-guanidine (104)

To a stirred solution of 540 mg (0.99 mmol) of the guanidine (103) in 0.6 ml of water and 1.0 ml of dioxan over a salt/ice bath was added 10 ml of 4M sodium hydroxide and 2.200 g (9.46 mmol - 50% pure) of isobornyl chloroformate (96)

in small alternate portions[38]. The alkalinity of the solution was maintained at pH 10-11. After a further hour, 20 ml of 1M citric acid was added, and the solution was extracted with ethyl acetate which was dried and evaporated to an oil (2.48 g). The oil was passed down a silica gel column (ether) to yield 309 mg (33 %) of the protected guanidine (104). ν_{max} 3350, 2950, 1740, 1690, 1640 cm^{-1}. ^1H n.m.r. δ_H (acetone-d_6) 0.35, s, 6H; 0.4, s, 6H; 0.5, s, 6H; 0.7 - 1.3, m (broad), 6H; 2.5, bs, 2H; 3.0, bs, 4H; 4.1, bs, 1H (exchanged by D_2O); 4.50, s, 2H; 6.8, s, 5H; 8.0, bs, 1H (exchanged by D_2O). ^{13}C n.m.r. δ_C(acetone-d_6) 11.7, 20.4, 34.1, 39.0, 41.2, 42.5, 45.8, 47.5, 49.6, 66.3, 84.7, 128.5, 129.1, 138.4, 153.8, 154.9, 157.1.

Attempted Preparation of N-(6-Aminohexyl)-N,N'-bis(isobornyloxy-carbonyl)guanidine (105)

To a stirred suspension of 8 mg of 5% palladium on charcoal [20% by weight of carbamate (104)] in 8 ml of methanol saturated with hydrogen, was slowly added 39 mg (0.063 mmol) of the benzyl carbamate (104)[115]. The solution was stirred for 5 h after addition, then filtered through a bed of celite and evaporated to an oil (33 mg). Only partial reaction had occurred, according to t.l.c., the presence of amine being confirmed by a positive ninhydrin test. The 33 mg of material was returned to the hydrogenator and stood over palladium in methanol saturated with hydrogen overnight. T.l.c. indicated a total of three products as well as unreacted benzyl carbamate (104) present. The oil (30 mg) was isolated in the above manner but the components

were not separated, nor identified. ^{1}H n.m.r. δ_H0.78, s; 0.85, s; 1.0, s; 1.1 - 2.1, m; 3.2, bs; 4.6, bs; 5.1; 7.3. ^{13}C n.m.r. δ_C 26.0, 26.9, 29.6, 33.5, 38,4, 45.0, 47.0, 49.1, 66.6, 84.5, 128.0, 128.1, 128.6, 154.4, 154.7, 156.7.

N-[6-(Benzyloxycarbonylamino)hexyl]guanidine (106)

To 5 mg of the protected guanidine (104) was added 0.5 ml of trifluoroacetic acid (Fluka). The mixture was heated at reflux for 5 min.[38]. T.l.c. of the cooled mixture indicated hydrolysis of the isobornyloxycarbonyl groups to produce the guanidine (106).

N-[6-Benzyloxycarbonylamino)hexyl]-N'-*p*-toluene-sulphonylguanidine (107)

This compound was prepared from the guanidine (103) according to the method of Ramachandran and Li[36], but with a chloroform work up. Purification of the oil by passage down a silica gel column (5% methanol in chloroform) gave a 48% yield of the pure protected guanidine (107). ν_{max} 3440, 3340, 2900, 1700, 1620, 1550, 810, 680, 560 cm^{-1}. ^{1}H n.m.r. δ_H 1.3, bs, 8H; 2.35, s, 3H; 3.15, m, 4H; 5.1, s, 2H; 5.2, bs, 1H (exchanged by D_2O); 6.3, m (broad), 2H (exchanged by D_2O); 7.15, d, 2H; 7.24, s, 5H; 7.65, d, 2H. ^{13}C n.m.r. δ_C 21.4, 26.0, 28.9, 29.6, 40.8, 40.9, 66.6, 125.9, 127.9, 128.1, 129.3, 136.7, 140.9, 142.1, 156.8.

N-(6-Aminohexyl)-N-*p*-toluenesulphonylguanidine (108)

(ia) Catalytic hydrogenation.

The same procedure as that devised for the attempted preparation of the guanidine (105) was used, based upon 62 mg of the benzyl carbamate (107). The course of the reaction was monitored by t.l.c. (2% methanol/chloroform and 20% (0.88) ammonia/methanol). After 9 h the hydrogenation was stopped and the product isolated as previously described. The volume change for the hydrogen consumed was ambiguous. The t.l.c. of the isolated oil revealed three ninhydrin positive components; one major (108) and two minor. ^{1}H n.m.r. δ1.22, bs, 8H; 2.28, s, 3H; 3.00, m, 4H; 3.8-6.7; broad, 5H (exchanged by D_2O); 7.10, d, 2H; 7.62, d, 2H.

(ib) Proton Transfer Hydrogenation[56].

A solution of 254 mg of the benzyl carbamate (107) in 3 ml methanol was added to 250 mg of 5% palladium in charcoal stirred in 1 ml of methanol, followed by 6 ml of 10% formic acid in methanol. The reaction was monitored by t.l.c. but no reaction occurred within 3 days.

(ii) Acid Hydrolysis.

The acid hydrolysis of the benzyl carbamate (62) was based on the method of Boissonnas[57].

To 88 mg (0.23 mmol) of the benzyl carbamate (107) was added 1 ml of 20% hydrogen bromide dissolved in anhydrous acetic acid (Aldrich; 40% hydrogen bromide in acetic acid was diluted with glacial acetic acid (AR) to give the cleanest product

and optimum yield). The oil slowly dissolved with stirring and bubbles evolved. The solution was stirred for 35 min, then 20 ml of ether was added. The product oiled out, therefore the ether and excess of hydrogen bromide and acetic acid were removed by evaporation at room temperature. The residue was triturated (3 x 5 ml) with ether to give a pale brown, water soluble, gummy solid, being the primary aminium bromide (108.HBr) (66 mg, 88%) which did not need further purification. ν_{max} 3400-2500 (many peaks corresponding to RNH_3^+), 2000-1920 (several peaks), 1675, 1620, 1490, 1150, 670, 580, 550. ^1H n.m.r. $\delta_H(D_2O)$ 1.4, bs, 8H; 2.41, s, 3H; 3.1, m, 4H; 7.40, d, 2H; 7.80, d, 2H. ^{13}C n.m.r. $\delta_C(D_2O)$ 21.5, 26.0, 26.1, 27.4, 28.6,40.3,41.9, 126.9, 130.7, 149.3, 153.8, 157.1.

N-[6-(Cyanoethylamino)hexyl]-N'-*p*-toluenesulphonylguanidine (109)

To a stirred solution 225 mg (0.57 mmol) of the aminium bromide (108.HBr) in 10 ml of methanol was added 50 mg (0.37 mmol) of potassium carbonate followed by 31 mg (0.57 mmol) of acrylonitrile (55). The solution was stirred for 3 days. The methanol was removed by evaporation, water (5 ml) was added then worked up with chloroform (3 x 15 ml) to afford an oil. The oil was passed down a silica gel column (10% methanol/chloroform) to yield 84 mg (51%) of the cyanoethylamine (109) ν_{max} 3460, 2950, 2250, 1630, 1590, 1530, 1240, 815, 680, 560 cm^{-1}. ^1H n.m.r. δ_H1.28, bs, 9H (1H exchanged by D_2O); 2.32, s, 3H; 2.50, m, 4H; 3.10, m,

4H; 6.4, bs, 3H(exchanged by D_2O); 7.18, d, 2H; 7.85, d, 2H. ^{13}C n.m.r. δ_C21.4, 26.3, 26.5, 29.0, 29.7, 41.1, 118.8, 125.9, 129.3, 140.8, 142.1, 156.9.

The impurity (eluted by 5% methanol/chloroform) was identified as the bis(cyanoethyl)amine (111). ν_{max} 2250 cm^{-1} ^1H n.m.r. δ1.3, bs, 8H; 2.2-3.3, m, 15H; 6.3, bs, 3H(exchanged by D_2O); 7.2, d, 2H; 7.9, d, 2H.

N-Cyanoethyl-N-[6-(N'-*p*-toluenesulphonylguanidino)hexyl]-acetamide (112)

A stirred solution of 65 mg (0.178 mmol) of the amine (109) in 1 ml of dichloromethane and 36 mg (0.356 mmol) of triethylamine was cooled over ice. A solution of 14 mg (0.178 mmol) of acetyl chloride in 2 ml of dichloromethane was slowly added to the amine. The solution was allowed to warm to room temperature and after 2 h, 8 ml of water was added and acidified with 2M hydrochloric acid to pH 3, followed by work up with chloroform (3 x 5 ml) to give 69 mg (95%) of the acetamide (112). ν_{max} 3350, 2950, 2250, 1650 (v. broad), 1550, 810, 680, 560, cm^{-1}. ^1H n.m.r. δ1.38, bs, 8H; 2.09, s, 3H; 2.40, s, 3H; 2.65, m, 4H; 3.4, m, 4H; 6.40, bs, 3H (exchanged by D_2O); 7.20, d, 2H; 7.70, d, 2H.

N-[(6-Cyanomethylamino)hexyl]-N'-(*p*-toluenesulphonyl)-guanidine (110)

(i) To a stirred solution of 609 mg (1.55 mmol) of the aminium bromide (108) and 450 mg (3.26 mmol) of potassium carbonate in 3 ml of HMPA[59] was slowly

added 140 mg (1.86 mmol) of chloroacetronitrile (79). The reaction was stirred overnight then heated at 75° for 5 h. The product was isolated by addition of 15 ml of water and extracted with ether (4 x 15 ml). The ether phase was backwashed twice with water, dried and evaporated to an oil, tentatively identified as the cyanomethylamine (110) (110 mg, 20%), ν_{max} 2240 cm^{-1}. ^1H n.m.r. δ_H 1.25, s, 8H; 2.30, s, 3H; 2.6, m, 4H; 3.1, m, 2H; 3.53, s, 2H; 6.45, s, 3H; 7.2, d, 2H; 7.7, d, 2H.

(ii) Synthesis of the cyanomethylamine (110) was also attempted in dimethylformamide, Me_2SO, and HMPA with the additional use of tetraethylammonium iodide. The products were isolated by extraction with ether after dilution of the reaction mixture with water. Only 10% recovery was achieved in each case.

(iii) Synthesis of the cyanomethylamine (110) was also attempted in benzene and ethanol with organic and inorganic bases, without success.

(iv) Synthesis of the cyanomethylamine (110) was also attempted *via* a formaldehyde-bisulphite addition complex according to the Strecker synthesis with the Knoevenagel-Bucherer modification[60]. An intractable blue gum, that was insoluble in water, chloroform, and methanol, formed.

(v) A second modification of the Strecker synthesis enabled the cyanomethylamine to be prepared[60]. To a concentrated aqueous solution at 216 mg (0.55 mmol)

of the aminium bromide (108), 35 mg (0.55 mmol) of potassium cyanide was added followed by 57 mg (0.72 mmol) of formaldehyde. The solution quickly went dark and the product oiled out after 20 min. The reaction was left overnight then worked up with chloroform (3 x 5 ml) to give 82 mg of an oil tentatively identified as the cyanomethylamine (110) (43%). ν_{max} 2240 (weak) cm^{-1}. ^1H n.m.r. δ_H1.22, bs, 8H; 2.32, s, 3H; 2.60, bt, 4H; 3.10, m, 2H; 3.50, s, 2H; 6.32, bs, 3H; 7.15, d, 2H; 7.67. d. 2H. ^{13}C n.m.r. δ_C21.4, 26.0, 27.0, 29.1, 37.2, 41.1, 48.6, 118.1, 125.9, 129.3, 140.8, 142.1, 156.8.

Attempted Preparation of N[6-(Cyanomethylamino)hexyl]-guanidine (83)

(i) By the method in part (iv) above, 6-aminohexyl-guanidine (74) was added to the formaldehyde-bisulphite complex. No reaction was evident after 48 h (t.l.c.).

(ii) By the method in part (v) above, only slight reaction had occurred (t.l.c.) after 48 h (t.l.c.).

Deodecanoyl Chloride (113)

Dodecanoyl chloride (113) was prepared from dodecanoic acid by the same method as that described for the preparation of 3,3-dimethylacryloyl chloride (56), b.p. 140-145° (18 mm). [lit. b.p. 145° (18 mm)][104].

Attempted Preparation of N-(6-Guanidinohexyl)-dodecanamide (114)

To a stirred solution of 1.7 g (4.1 mmol) of aminohexylguanidine (74) and 1.0 g (12.0 mmol) of sodium bicarbonate in 10 ml of water and 10 ml of toluene chilled over a salt/ice bath, was slowly added 1.98 g (8.2 mmol) of dodecanoyl chloride (113) in 5 ml of toluene. The solution was stirred overnight at room temperature. The two phases were separated and the aqueous phase was extracted with chloroform (3 x 5 ml). The product in the organic extract had a high R_f compared to the guanidine (74), but it was negative to the Sakaguchi test.

Attempted Preparation of N-[6-(*p*-Toluenesulphonylguanidino)-hexyl]dodecanamide (115)

(i) To a stirred solution of 95 mg (0.24 mmol) of the aminium bromide (108) in 3 ml of pyridine over ice was slowly added 53 mg (0.24 mmol) of dodecanoyl chloride (113). The solution was allowed to warm to room temperature after addition of the acyl chloride (113) and left overnight. Addition of water (10 ml) followed by a chloroform work up, afforded dodecanoic acid, m.p. 44-47° (lit m.p. 44°)[104], mixed m.p. 44-47°.

(ii) Attempts to prepare the amide (115) by means of the reagent 1-methyl-2-chloropyridinium iodide (116) according to the method of Mukaiyama *et al.*[62], led only to an intractable mixture of compounds. No evidence of the formation of an amide in the product mixture could be established, (i.r.).

Attempted Preparation of N-(6-Aminohexyl) -N'-nitroguanidine (117)

To 2.00 g (9.66 mmol) of aminohexylguanidine (74) was added 3.5 ml of concentrated sulphuric acid, followed by 1.02 g (9.66 mmol) ammonium nitrate according to the method of Hayakawa *et al.*[63]. After standing for 15 min the solution was tipped onto ice and neutralized with aqueous ammonia. The neutral solution was worked up in the usual manner but only 100 mg of a brown indeterminate solid was isolated.

N-(Cyanomethyl)-1,6-diaminohexane (118)

To a stirred solution of 813 mg (7.0 mmol) of 1,6-diaminohexane and 98 mg (7.0 mmol) of potassium carbonate in 10 ml of benzene (or ethanol) was slowly added 529 mg (7.0 mmol) of chloroacetonitrile (79) in 10 ml of benzene (or ethanol), followed by heating at reflux for 0.5 h. The crude product was isolated as an oil by dichloromethane extraction from 3% aqueous sodium hydroxide (0.48 g, 44%). Re-extraction of the aqueous phase with 10% 2-propanol/chloroform yielded 0.65 g (3.6 mmol) of unreacted 1,6-diaminohexane.

The N-(cyanomethyl)-1,6-diaminohexane (118) was separated from the 1,6-bis-product by dry column chromatography on silica gel (Brockmann Act III, 30 mm) using methanol/ammonia (5:1) as eluent (0.36 g, 34%). ν_{max} 3300, 2250, 1470, 1120, 870 cm^{-1}. ^{1}H n.m.r. δ_H 1.40, s, 8H; 1.97, s, 3H (exchanged by D_2O); 2.72, t, 4H; 3.60, s, 2H. ^{13}C n.m.r. δ_C 26.5, 26.8, 28.8, 31.0, 36.9, 41.2, 48.8, 119.8.

Attempted purification by ion exchange chromatography on Zeo-Karb 225(H^+) led to many unidentifiable products. Also, decomposition occurred when purification by vacuum distillation (0.5 mm) was attempted.

S-Methylisothiouronium iodide (119)

This compound was prepared from the sulphate (75) according to the method of Lespagnol *et al.*[64] (83%), m.p. 111-114° (lit. m.p. 117°) ^{13}C n.m.r. $\delta_C(H_2O)$ 14.2, 173.8.

Attempted Preparation of N-[6-(Cyanomethylamino)hexyl]-guanidinium sulphate (83)

(i) To a suspension of 539 mg (1.94 mmol) of the thiourea (75) in ethanol was added 300 mg (1.94 mmol) of amine (118). The mixture was stirred at room temperature for 5 h then heated at reflux for 3 h, after which the suspension was removed by filtration and the solution evaporated to an oil. The solid residue was identified as unreacted thiourea (75) [m.p. 272°(dec)] and the oil was unreacted amine (118)(^1H n.m.r., ^{13}C n.m.r.). Some oxidation of the nitrile in the compound (118) was detected by i.r. (ν_{max} 1660 cm^{-1}).

(ii) The reaction was repeated in 20 ml of water but it was stirred overnight at room temperature. Little reaction had occurred, according to t.l.c., so the mixture was heated at reflux for 2 h. Four guanidino compounds were visualized by Sakaguchi reagent after t.l.c. [Riedel-de Haën foil backed cellulose CE: eluent; butanol/pyridine/acetic acid/water (9:1:1:4)]. The solution was evaporated to an oil

(0.61 g) and passed down an ion exchange column [Zeo-Karb 225(H^+),4M HCl]. The major component positive to the Sakaguchi reagent was isolated from the column (183 mg, 42%). ν_{max} 3400, 3160, 1690, 1650, 1620, 1100 cm^{-1}. ^{13}C n.m.r. $\delta(H_2O)$ 26.0, 26.2, 28.5, 35.2, 42.0, 44.0, 48.9, 157.7.

(iii) To a solution of 300 mg (1.94 mmol) of amine (118) in 10 ml of ethanol under nitrogen, was added 181 mg (0.97 mmol) of the pyrazole (76). After heating the mixture at reflux for 2 h, it was evaporated and triturated with ether to yield 121 mg of a gummy solid (51%) ν_{max} 3300, 1690, 1640, 1100 cm^{-1}. ^{13}C n.m.r. $\delta_C(H_2O)$ 26.0, 26.2, 27.6, 28.5, 40.6, 42.0, 115.6, 157.8.

Attempted Preparation of N-[6-(Cyanomethylamino)hexyl]guanidinium-iodide (88)

To a solution of 64 mg (0.41 mmol) of amine (118) in 5 ml of ethanol was added 90 mg (0.41 mmol) of the iodide (119). The salt dissolved and the mixture was stirred at room temperature for 48 h. Visualization of the t.l.c. by Sakaguchi reagent showed the presence of two guanidino compounds. The ethanol was removed by evaporation and purification was attempted by dry column chromatography [Brockmann silica gel; methanol/ ammonia (0.88) / water (4:1:1) followed by 1M HCl] without separation. Ion exchange chromatography [Zeo-Karb 225(H^+)] (4M) promoted oxidation of the nitrile. ^{13}C n.m.r. $\delta_C(H_2O)$ 25.9, 26.0, 26.2, 27.0, 28.5, 35.2, 42.0, 44.0, 47.8, 48.9, 157.7, 159.1.

N-(*p*-Toluenesulphonyl)-S-methylisothiourea (120)

This compound was prepared according to the method of Cox and Sprague[65] (6%), m.p. 117-118° (lit. m.p. 118-119°) ν_{max} 3450, 3350, 1600, 1140, 580 cm^{-1}. ^1H n.m.r. δ_H2.38, s, 3H; 2.40, s, 3H; 7.0, bs, 2H (exchanged by D_2O); 7.3, d, 2H; 7.8, d, 2H. ^{13}C n.m.r. δ_C14.0, 21.5, 126.4, 129.4, 139.2, 143.1, 158.0.

The reaction was repeated using sodium carbonate and sodium bicarbonate as base without improving the yield. A two-phase reaction with aqueous benzene yielded 19% of the product (120). When pyridine or triethylamine were used in benzene no thiourea (120) was isolated.

Attempted Preparation of N-[6-(Cyanomethylamino)hexyl] N'-(*p*-toluenesulphonyl)guanidine (110)

To a solution of 146 mg (0.94 mmol) of amine (118) in 5 ml of ethanol was added the thiourea (120)(200 mg, 0.94 mmol). No reaction was observed by t.l.c. within 3 days, only the two starting compounds being detected. The solvent was removed by evaporation and the residue (quantitative) analysed. ^1H n.m.r. δ_H(methyl ratios, 1:1) 2.38, 2.40. Heating at reflux did not yield any guanidine (110), only slow decomposition of the amine (118) occurred.

Attempted Preparation of N-(6-Aminohexyl)diphenylphosphinamide (126)

To a chilled and stirred solution of 2.6 g (21.9 mmol) of 1,6-diaminohexane in 30 ml of dichloromethane was slowly added 2.6 g (11 mmol) of diphenylphosphinyl chloride (54)

in 20 ml of dichloromethane. The mixture was stirred overnight at room temperature, then acidified (1M HCl) and extracted with dichloromethane (2 x 10 ml). The aqueous phase was basified with 10% aqueous sodium hydroxide and extracted with 10% 2-propanol/chloroform.

The dichloromethane solution was dried and evaporated to a gum and tentatively identified as 1,6-bis(diphenylphosphinamido)hexane (124) (2.8 g, 98%). ν_{max} 3400, 2950, 2600, 1170, 1100, 750, 730 cm^{-1}. ^1H n.m.r. δ_H1.3, s, 8H; 3.3, m, 4H; 6.7-7.5, m, 20H.

Attempted Preparation of N-(6-Aminohexyl) diethyl phosphoramidate (127)[44]

The method identical to the attempted preparation of the amine (126) was used except diethyl chlorophosphate (66) (Aldrich) was substituted for the diphenylphosphinyl chloride (54)[22]. The product was isolated by filtration [3.38 g, 50% based on the product (127) or 68% based on the bis-product (125)]. The product was found to be positive to ninhydrin, m.p. (acetone/water) 170-210°. The organic extract contained unreacted 1,6-diaminohexane and a trace of a phosphoramidate (127) which was not isolated.

Attempted Preparation of N-Triphenylmethyl-1,6-diaminohexane (129)

To a stirred solution of 2.415 g (20.78 mmol) of 1,6-diaminohexane and 1.436g(10.39 mmol) of potassium carbonate in 25 ml of ethanol free chloroform cooled to 0° was slowly added 5.79 g (20.78 mmol) of triphenylchloromethane (123) (BDH) in 10 ml of chloroform[116].

A precipitate formed which was isolated after 2 h by filtration then washed with a little cold chloroform. The precipitate was suspended in water, heated over steam, then the hot suspension again isolated by filtration and washed with a little hot water to give 2.55 g of air dried residue, negative to ninhydrin, identified as N,N'-bis(triphenylmethyl)diaminohexane (128), m.p. 181°. ^{1}H n.m.r. δ_H 1.32, bs, 8H; 1.50, s, 3H; 2.16, bt, 4H; 7.0-7.4, m, 30H. ^{13}C n.m.r. δ_C 27.3, 30.8, 43.5, 70.9, 126.1, 127.7, 128.7, 146.4.

The chloroform filtrate was extracted with a little water and worked up to give 6.452 g of a mixture of the bis-product (128) and the monotriphenylmethyl compound (129), identified (but not isolated) by comparison of the ^{1}H n.m.r. spectra integrals and ^{13}C n.m.r. peaks. ^{13}C n.m.r. δ26.8, 27.3, 30.8, 33.6, 42.1, 43.5, 70.9, 126.1, 127.7, 128.6, 146.3.

Attempted Preparation of N-Cyanomethyl-N'-triphenylmethyl-1,6-diaminohexane (130)

To a stirred solution of 1.75 g (11.3 mmol) of N-cyanomethyl-1,6-diaminohexane (118) at 0° in 13 ml of ethanol free chloroform was added 1.20 g (11.9 mmol) of triethylamine followed by 3.15 g (11.13 mmol) of triphenylchloromethane (123). There was no detectable temperature change so the mixture was stirred overnight at room temperature. An intractable precipitate had formed which was insoluble in all the normal solvents and negative to the ninhydrin test. ν_{max} aromatic region only.

N-(*tert*-Butyloxycarbonyl)-1,6-diaminohexane (131)

This compound was prepared according to the method of Stahl *et al.*[26] (58%), m.p. 162-163° (lit. m.p. 162.5-163°). ^{1}H n.m.r. δ_H1.42, bs, 17H; 2.8-3.3, m, 4H; 4.5-6.0, bs, 4H (exchanged by D_2O). ^{13}C n.m.r. δ_C26.1, 26.3, 27.4, 28.5, 29.4, 40.2, 40.7, 81.7, 156.1.

Attempted Preparation of N-Benzyloxycarbonyl-1,6-diaminohexane (133)

(i) To an ice cold, stirred solution of 3.17 g (27.3 mmol) of 1,6-diaminohexane in 9 ml of 1M sodium hydroxide, was added simultaneously and dropwise 2.32 g (13.6 mmol) of benzyl chloroformate (94), and 3.4 ml of 4M sodium hydroxide. When the solution had warmed to room temperature, the precipitate was isolated by filtration, washed with a little cold water and vacuum dried (1 mm). The precipitate was identified as the bis product (132) (3.80 g), m.p. 122.5 - 123.5°. ν_{max} 3350 (sharp), 1690, 1530, 1250, 780, 750, 730, 700 cm^{-1}. ^{1}H n.m.r. δ 1.32, bs, 8H; 3.10, m, 4H; 4.8, bs, 2H; 5.08, s, 4H; 7.30, s, 10H. The aqueous solution was extracted with ethyl acetate (4 x 15 ml) which was dried and evaporated to an odourous oil identified as unreacted 1,6-diaminohexane (t.l.c.).

(ii) The reaction was repeated in dichloromethane over ice without added base, but with equimolar portions of reagents. A precipitate formed which was isolated by filtration in quantitative yield. The t.l.c.,

however, was identical to that of preparation (i), m.p. 122-123°, mixed m.p. 122-123°

N-(*tert*-Butyloxycarbonyl)-N'-cyanomethyl-1,6-diaminohexane (135)

A solution of 600 mg (2.37 mmol) of the amine (131), 179 mg of chloroacetonitrile (79) and 719 mg (7.11 mmol) of triethylamine in 5 ml of ethanol was heated at reflux for 4h. Evaporation of the ethanol, dissolution in water following by a chloroform work up, afforded 316 mg (52%, but not optimized) of the cyanomethylamine (135), b.p. 139-143° (0.005 mm). (Found: M^+, 255.1947. $C_{13}H_{25}N_3O_2$ requires 255.1947). ν_{max} 3350, 2950, 2250 (v. weak), 1700, 1530, 1170 cm^{-1}. ^1H n.m.r. δ_H 1.42, bs, 18H; 2.70, m, 2H; 3.04, m, 2H; 3.57, s, 2H; 4.70, bs, 1H (exchanged by D_2O). ^{13}C n.m.r. δ_C 26.2, 26.4, 28.2, 29.0, 29.7, 36.9, 40.1, 48.4, 78.7, 117.6, 155.8.

The reaction did not occur after extended stirring at room temperature. Also, attempted preparationsusing inorganic bases (potassium carbonate and sodium bicarbonate according to the method of Sidhu *et al.*[47], lead to many decomposition products attributable to hydrolysis of the *tert*-butyloxycarbonyl group.

N-(*tert*-Butyloxycarbonyl)-N'-cyanoethyl-1,6-diamino-hexane (136)

The amine (131) was converted to the free base with 10% aqueous sodium hydroxide (15 ml) and isolated by a chloroform work up.

The *in vacuo* dried amine (131), 718 mg (3.32 mmol), and 176 mg (3.32 mmol) of acrylonitrile (55) (Aldrich) in 5 ml of ethanol were stirred at room temperature for 48 h before the reaction was completed (t.l.c.). Evaporation of the solvent afforded the cyanoethylamine (136) as a waxy solid in quantitative yield, m.p. 39-39.5°, b.p. 142-147° (0.005 mm) (Found: M^+, 269.2103. $C_{14}H_{27}N_3O_2$ requires 269.2100). ν_{max} 3400, 2250, 1680, 1520 cm^{-1}. ^1H n.m.r. δ_H 1.41, bs, 18H; 2.7, m, 4H; 3.0, m, 4H; 4.75, bs, 1H. ^{13}C n.m.r. δ_C 18.5, 26.4, 26.6, 28.3, 29.7, 29.8, 40.4, 44.9, 48.9, 78.7, 118.6, 155.9.

Attempts to prepare the cyanoethylamine (136) from the aminium chloride (131) in the presence of inorganic bases were successful only in very low yield[47].

SECTION 2 : SYNTHESIS OF THE ACARNIDINES

N-(Propyl)aminobutane (140)

To a stirred solution of 1.00 g (13.7 mmol) of aminobutane in 20 ml of tetrahydrofuran and 1 g of molecular sieves (4Å, Sigma) was added 0.975 g (13.7 mmol) of propanal (Aldrich). The reaction was monitored by ^{1}H n.m.r. (in the tetrahydrofuran solvent) and after 12 min the formyl proton was no longer observed (δ_H=9.72 for CHO) but a broad triplet had appeared at δ_H=7.57 ppm. The tetrahydrofuran was removed by evaporation and the residual oil was taken up in 25 ml of ethanol. A solution of 0.30 g (7.89 mmol) of sodium borohydride dissolved in 5 ml of ethanol was added with swirling. The solution warmed spontaneously and effervescence occurred. The solution was heated at reflux for 1.5 h, then evaporated to 8 ml; water was added and 0.55 g of the amine was extracted with ether (34%). The yield was not optimized. ν_{max} 3350, 1600 cm^{-1}. ^{1}H n.m.r. $\delta_H(CCl_4)$ 0.88, t, 6H; 1.4, m, 7H(1H exchanged by D_2O); 2.5, bt, 4H. ^{13}C n.m.r. δ_C 10.2, 12.6, 18.5, 19.1, 27.0, 46.9, 48.7.

Attempted Preparation of N-(6-Propylaminohexyl)guanidine (141)

To a solution of 0.88 g (1.84 mmol) of aminohexylguanidinium tetraphenylborate (84) in 10 ml of tetrahydrofuran, was added 0.3 g of molecular sieves (4Å) followed by 0.11 g (1.90 mmol) of propanal. Disappearance of the formyl proton (observed by ^{1}H n.m.r.) was slow and enforced the solution to be left overnight. The solution was

filtered, then evaporated to an oil, to which 10 ml of ethanol containing 139 mg (3.68 mmol) of sodium borohydride was added with swirling. When the vigorous bubbling had ceased, the solution was heated at reflux for 15 min. The solution was evaporated to an oil and acidified with 1% hydrochloric acid (7 ml). A white gelatinous precipitate formed which was removed by filtration (229 mg). The filtrate was extracted with tetrahydrofuran which was dried and evaporated to an oil (1.260 g) and analysed. ^{13}C n.m.r. $\delta_C(CD_3OD)$ 25.8, 26.4, 26.6, 28.9, 29.4, 41.6, 115.6, 119.2, 122.2, 125.7, 125.8, 126.0, 126.1, 127.7, 129.4, 134.4, 136.6, 136.7.

N-(*tert*-Butyloxycarbonyl)-N'-propyl-1,6-diaminohexane (142)

A suspension of 309 mg (1.22 mmol) of the amine (131), 0.3 g of molecular sieves (4Å) and 186 mg (1.34 mmol) of anhydrous potassium carbonate was stirred in 5 ml of chloroform for 15 min before 78 mg (1.34 mmol) of propanal was added in one portion. The reaction was monitored by ^1H n.m.r. After 4 h the solution was filtered then evaporated to an oil and redissolved in 10 ml of ethanol. A solution of 59 mg (1.59 mmol) of sodium borohydride, dissolved in 3 ml of ethanol, was added with swirling, then after the evolution of hydrogen had diminished the solution was heated at reflux for 0.5 h. The ethanol was removed by evaporation and 5 ml of water was added and partitioned with ether (3 x 10 ml), dried and evaporated to 310 mg of an oil (quantitative). ν_{max} 3400,

1700, 1160 cm^{-1}. ^{1}H n.m.r. δ_H0.82, t, 3H; 1.32, bs, 19H; 2.5, bt, 5H; 3.0, m, 2H; 5.42, bs, 1H (exchanged by D_2O). ^{13}C n.m.r. δ_C11.3, 19.7, 26.1, 26.2, 26.5, 28.4, 29.6, 40.3, 47.7, 49.5, 78.4, 156.1. Mass spectrum (c.i.) m/z 441 (30%, MH^+), 385 (88, $MH^+-C_4H_8$), 367 (23, $MH^+-C_4H_{10}O$), 341 (100, $MH^+-CO_2-C_4H_8$).

N-[6-(*tert*-Butyloxycarbonylamino)hexyl]-N-propyldodecanamide (143)

To a stirred solution of 130 mg (0.50 mmol) of the secondary amine (142) and 102 mg (1.0 mmol) of triethylamine in 6 ml of dichloromethane was slowly added 111 mg (0.50 mmol) of dodecanoyl chloride (113) in 4 ml of dichloromethane. After 3 h the solution was extracted with water (4 x 5 ml), dried and evaporated to an oil which was identified as the dodecanamide (143) (222 mg, 93%). ν_{max} 3350, 2920, 1710, 1640 cm^{-1}. ^{1}H n.m.r. $\delta_H(CCl_4)$ 0.90, bt, 6H; 1.34, s, 18H; 1.43, bs, 11H; 1.5-1.9, m, 6H; 2.22, bt, 2H; 2.8-3.4, m, 6H; 5.4, bs, 1H (exchanged by D_2O).

N-(6-Aminohexyl)-N-propyldodecanamide (144)

Trifluoroacetic acid (1.5 ml) was added to 202 mg (0.46 mmol) of the carbamate (143) with swirling[75]. Gas evolution was observed as the oil slowly dissolved. The solution was stirred for 50 min before addition of 20 ml of water and worked up with dichloromethane (2 x 10 ml) to yield 208 mg (quantitative) of the aminium trifluoroacetate (144.CF_3COOH). ν_{max} 3350, 3050, 2950, 2550, 1780, 1740, 1680, 1630, 1160 cm^{-1}. The oil was redissolved in

5 ml of 2.5M aqueous sodium hydroxide and extracted with dichloromethane (3 x 5 ml) to yield the more easily analysable amine (144) (135 mg, 87%). ν_{max} 3340, 2940, 1745, 1645, 1470 cm^{-1}. ^{1}H n.m.r. δ_H 0.90, t, 6H; 1.29, bs, 18H; 1.45-2.85, m, 9H; 2.22, m, 4H; 3.25, m, 4H. ^{13}C n.m.r. δ_C 11.3, 11.4, 14.1, 22.4, 22.7, 25.0, 25.6, 26.7, 26.8, 29.2, 29.4, 29.6, 31.9, 33.2, 34.1, 36.9, 45.8, 47.5, 48.0, 49.7, 172.8. The amine (144) was impure (approximately 85% pure by t.l.c.).

N-(6-Guanidinohexyl)-N-propyldodecanamide (145)

A solution of 128 mg (0.38 mmol) of the amine (144) and S-methylisothiouronium iodide (119) in 5 ml of ethanol were stirred for 72 h. The reaction was monitored by t.l.c. The reaction was ended by the addition of 25 ml of 1% aqueous hydriodic acid (Merck) and extraction with chloroform. The work up was slowed by the formation of an emulsion, but the impure guanidine (145) was isolated as an oil (158 mg, 82%). The guanidine (145) was subsequently purified by gel permeation chromatography (*vide infra*: the general method for synthesizing the acarnidines), 37% yield of pure guanidine (145). (Found: (h.r.f.a.b.) MH^+, 383.3760. $C_{22}H_{47}N_4O$ requires 383.3750). ν_{max} 3350, 3200, 2950, 1665, 1650, 1630, 1470 cm^{-1}. λ_{max} (CH_3OH) 218 nm (ε 15 000) (Inflection at 207 nm). ^{1}H n.m.r. δ_H 0.90, t, 6H; 1.25, s, 15H; 1.50, s, 12H; 2.30, t, 2H; 3.30, m(broad), 6H; 6.8, bs, 3H (exchanged by D_2O); 7.3, bs, 2H (exchanged by D_2O). ^{13}C n.m.r.

δ_C11.1, 14.0, 22.1, 22.5, 25.5, 25.8, 26.1, 27.1, 28.1, 29.2, 29.5, 31.7, 33.0, 42.1, 46.1, 50.0, 157.2, 173.6.

Attempted guanidination *via* S-methylisothiouronium sulphate (75) produced a number of impurities besides the desired product, according to t.l.c. Heating at reflux in ethanol gave several ninhydrin test positive products, whereas in water, with stirring at room temperature, gave little material positive to the Sakaguchi or ninhydrin tests, according to t.l.c.

N-(2-Hydroxyethyl)-3,3-dimethylacrylamide (146)

To a vigorously stirred solution of 18.48 g (0.304 mol) of 2-aminoethanol (Ajax) in 200 ml of alcohol free chloroform in a salt/ice bath was slowly added a solution of 16.32 g (0.138 mol) of 3,3-dimethylacryloyl chloride (56). When the addition was completed the solution was allowed to warm to room temperature. Cold 1M hydrochloric acid in saturated brine was added until the solution was acidic. The chloroform solution was removed and the aqueous phase was washed twice more (50 ml) with 10% 2-propanol/chloroform. The combined organic extracts were again washed with 1M hydrochloric acid in brine which was backwashed with 10% 2-propanol/chloroform. The organic solution was then washed with brine, saturated sodium carbonate solution and brine again, with backwashing, then dried and evaporated to an oil (17.56 g, 88%) identified as the amide (146), b.p. 104-111° (0.005 mm). (Found: M^+, 143.0976. $C_7H_{13}NO_2$ requires 143.0946). ν_{max} 3325,

3100, 2950, 1670, 1630, 1550 cm^{-1}. ^{1}H n.m.r. δ_H1.81, s, 3H; 2.16, s, 3H; 3.45, m, 2H; 3.62, m, 2H; 4.60, bs, 1H (exchanged by D_2O); 5.61, s, 1H; 6.99, bt, 1H (exchanged by D_2O). ^{13}C n.m.r. δ_C19.3, 26.6, 41.3, 60.8, 118.1, 150.4, 168.1.

The amide (146) was miscible with water and immiscible with ether. When a trace of water was present during the acylation, the proportion of amido-ester O-[2-(3,3-dimethylacrylamido)ethyl]3,3-dimethylacrylate (147) became substantial. (Found: M^+, 225.1365. The amido-ester, $C_{12}H_{19}NO_3$ requires 225.1323). δ_H4.13, t. The ester could by hydrolysed with methanolic sodium hydroxide. [See preparation of the amidopropanol (139)].

Attempted Preparation of N-(2-Oxoethyl)-3,3-dimethylacrylamide (148)

(i) Jones' oxidation[76].

Jones' reagent was prepared according to the method of Djerrasi, Engle and Bowers[76].

Jones' reagent (1.38 ml) was slowly added to a solution of 528 mg (3.69 mmol) of the alcohol (146) dissolved in 3 ml of acetone. The reaction was quenched when the solution turned green by addition of 5 ml of brine and 5 ml of ether. The mixture was extracted with ether (3 x 6 ml), then dried and evaporated to an oil (116 mg, 22%) which was a mixture of four compounds (t.l.c.). The reaction was repeated at 0° but without success. ν_{max} 1730, 1670 cm^{-1}.

(ii) Chromium trioxide-pyridine complex oxidation[77].

Chromium trioxide (dried over phosphorus pentoxide) (558 mg, 5.58 mmol) was added to a stirred solution of 882 mg (11.2 mmol) of pyridine in 2.5 ml of dichloromethane. A brown suspension formed in the burgundy solution. Stirring was continued for 15 min then a solution of 133 mg (0.93 mmol) of the alcohol (146) in 1 ml of dichloromethane was added at once and a black tarry deposit rapidly formed. The solution was stirred a further 15 min. The solution was decanted and the residue washed with 10 ml of ether. The combined organic extracts were washed with 10 ml of 5% aqueous sodium hydroxide, then 1% hydrochloric acid, 5% aqueous sodium bicarbonate, brine then dried and evaporated to an oil (22 mg, 17%). Many products were indicated by t.l.c. ^{1}H n.m.r. (no formyl proton). The reaction was repeated but the time after addition of the alcohol was reduced to 6 min; no change in the product mixture was observed.

(iiia) Pyridinium chlorochromate oxidation.

Pyridinium chlorochromate was prepared according to the method of Corey and Suggs[78].

The alcohol (146) (523 mg, 3.66 mmol), dissolved in 1 ml of dichloromethane, was added to the chromium complex suspended in 10 ml of dichloromethane and stirred for 45 min. Ether (4 x 10 ml) was added and the supernatant was decanted. The combined organic extracts were dried and evaporated to a greenish oil (207 mg, 40%).

Three compounds were identified by t.l.c. ν_{max} 3250, 1730, 1670, 1630 cm^{-1}. The reaction was repeated (time of reaction = 1.5 h) and the major products identified as a mixture of the aldehyde (148) and the corresponding acid. ν_{max} 3300, 3250, 3200, 1730, 1680, 1640 cm^{-1}. ^1H n.m.r. δ_H1.8, s, 3H; 1.9, s, 3H; 2.1, s, 3H; 2.2, s, 3H; 3.6, m, 2H; 4.2, m, 2H; 5.6, s, 1H; 5.8, s, 1H; 6.0-7.0, bd, 2H (exchanged by D_2O); 9.2, s, 1H (exchanged by D_2O); 9.3, s, 1H; 9.7, bs, 1H (exchanged by D_2O).

(iiib) Pyridinium chlorochromate on alumina oxidation.

Pyridinium chlorochromate on alumina was prepared according to the method of Cheng, *et al.*[79]. A yield of 69% was achieved by performing this reaction on a support, however no formyl proton was detected by ^1H n.m.r.

(iiic) Buffered pyridinium chlorochromate.

The reaction of (iiib) above was repeated with the addition of 20 mole per cent of sodium acetate. The solution was worked up after 1.5 h but gave a lower R_f product by t.l.c.

(iv) Chromium trioxide in HMPA oxidation.

Chromium trioxide (716 mg, 7.16 mmol) was slowly added to 1.1 ml of stirred HMPA[80]. After standing for 1 h, 512 mg (3.58 mmol) of the alcohol (146) was added and the solution (monitored by t.l.c.) was stirred for 6 h.

The solution was ultimately left overnight after which an intractable gum had formed.

(v) Potassium dichromate in dimethylsulphoxide and sulphuric acid oxidation[81].

To a stirred solution of 1.065 g (3.62 mmol) of potassium dichromate and 518 mg (3.62 mmol) of the alcohol (146) in 10 g of dimethylsulphoxide, was slowly added 0.72 ml (10 mmol) of 98% sulphuric acid. The reaction was heated at 70° until a green colour formed then the solution was poured onto ice and brine (20 ml) and extracted with 2% 2-propanol/dichloromethane (3 x 15 ml) to yield 98 mg of an oil. ν_{max} 3000, 1730, 1680, 1650 cm^{-1}. ^1H n.m.r. δ_H2.0, s, 6H; 2.3, s, 6H; 5.5, s, 1H (exchanged by D_2O); 5.78, s, 1H; 9.0, s, 1H (exchanged by D_2O); 9.2, s, 1H; 9.5, bs, 1H (exchanged by D_2O). A solid (64 mg) sublimed from the oil but its i.r. and ^1H n.m.r. spectra were identical to the spectra of the oil.

(vi) *tert*-Butyl chromate oxidation.

tert-Butyl chromate was prepared according to the method of Sharpless *et al.*[82].

To a *tert*-Butyl chromate solution was added 507 mg (3.35 mmol) of the alcohol (146) in 4 ml of dichloromethane. The solution rapidly turned brown but stirring was continued for 2 h. Methanol (2 ml) was added, then the organic solution was worked up to afford 114 mg (23%) of product, in which crystals slowly formed. ^1H n.m.r. δ_H1.79, s, 3H;

1.90, s, 3H; 2.02, s, 3H; 2.20, s, 3H; 3.5, bs, 2H; 4.70, bs, 2H; 5.60, s, 1H; 5.75, s, 1H; 5.8-6.5, bs, 1H (exchanged by D_2O); 9.1, s, 1H (exchanged by D_2O); 9.2, s, 1H; 9.7, bs, 1H (exchanged by D_2O).

The product was washed with 5% aqueous sodium bicarbonate but no change was noted by ^1H n.m.r.

(vii) Fetizon oxidation.

Fetizon reagent was prepared according to the method described by Fetizon[83].

Fetizon reagent (5.98 g) was added to a solution of 505 mg (3.53 mmol) of the alcohol (146) in 20 ml of acetonitrile. The suspension was heated at reflux for 40 h, with periodic monitoring by t.l.c. The silver slowly reduced, but after work up 382 mg of product, identified as an acid, was isolated. ν_{max} 3350 (v. strong), 1730 (v. strong), 1670, 1640 cm^{-1}.

(viiia) Moffat oxidation with pyridinium trifluoroacetate.

A solution of 560 mg (3.92 mmol) of the alcohol (146) in 2.00 g (16 mmol) of dimethylsulphoxide and 3 ml of benzene containing 2.256 g (12 mmol) of dicyclohexylcarbodiimide was prepared. Pyridinium trifluoroacetate[84,85] (378 mg, 2 mmol) was added with swirling and the reaction was left overnight. The solution was diluted with 10 ml of ethyl acetate and 469 mg (16 mmol) of oxalic acid was added. After gas evolution the urea was removed by filtration and the organic solution was washed with water

(3 x 10 ml) then dried and evaporated to an orange oil which solidified on standing. T.l.c. indicated only 50% reaction. ν_{max} 3350, 1720 (v. weak), 1680 cm^{-1}.

(viiib) Moffat oxidation with orthophosphoric acid[84].

This reaction followed (viiia) above, except that pyridinium trifluoroacetate was substituted by orthophosphoric acid. The reaction was followed by t.l.c. for 24 h. There was a gradual formation of products at higher R_f. ^1H n.m.r. δ(neither C<u>H</u>O nor COO<u>H</u> protons were evident).

(ix) N-Chlorosuccinimide oxidation[88].

To 2.037 g (15.2 mmol) of N-chlorosuccinimide in 30 ml of toluene at 0°, a solution of thioanisole in 20 ml of dichloromethane was added dropwise. The stirred solution was cooled to -25° in a dry ice/carbon tetrachloride bath and 485 mg (3.39 mmol) of the alcohol (146) in 10 ml of dichloromethane was slowly added. Vigorous stirring was continued for 2 h at -25°, then 3.08 (30.5 mmol) of triethylamine was slowly added. The solution was allowed to warm for 5 min before 10 ml of ethyl acetate was added. The organic solution was washed with cold 1% hydrochloric acid (5 ml) and water (2 x 3 ml), then dried and evaporated to an oil of lower t.l.c. R_f than the alcohol. ^1H n.m.r. (no formyl proton detected).

(x) Dimethylsulphoxide, pyridine-sulphur trioxide oxidation.

The pyridine-sulphur trioxide complex was prepared according to the method of Fieser[86], m.p. 172-174° (lit. m.p. 175°).

Pyridine-sulphur trioxide (2.054 g, 12.9 mmol) in 12 ml of dimethylsulphoxide was added to a stirred solution of 616 mg (4.31 mmol) of the alcohol (146), 12 ml of dimethylsulphoxide and 2.74 g (30.1 mmol) of triethylamine. Stirring was maintained for 1 h before 20 ml of dichloromethane was added. The organic solution was washed with 50% saturated brine (4 x 10 ml) then dried and evaporated to a relatively non-polar oil shown to be a mixture of three compounds by t.l.c. ν_{max} 1660 cm^{-1}.

(xi) Dimethylsulphoxide/oxalyl chloride oxidation[87].

A solution of 8 ml of dichloromethane and 0.33 ml (3.6 mmol) of oxalyl chloride was cooled to -70° (dry ice/acetone) before the rapid addition of 0.56 ml (7.22 mmol) of dimethylsulphoxide dissolved in 1.64 ml of dichloromethane. After stirring for 2 min, 469 mg (3.28 mmol) of the alcohol (146) dissolved in 3.3 ml of dichloromethane was added within 5 min with stirring for a further 15 min. Triethylamine (2.3 ml, 16.4 mmol) was added in about 5 min and the reaction mixture was stirred for another 5 min before allowing the solution to warm to room temperature. The reaction mixture was washed with brine (5 ml), 1% hydrochloric acid in brine (2 x 25 ml),

brine (10 ml), 20% (w/w) aqueous sodium bicarbonate (10 ml) and brine, with backwashing each time using dichloromethane (2 x 2 ml) before drying and evaporation to an oily mixture (243 mg, 53%) containing some aldehyde (148). ν_{max} 2740, 1730 (weak), 1660 cm^{-1}. ^1H n.m.r. δ_H9.57 (the integral was 33% of the expected integral when compared to the other peaks in the spectrum). The aldehyde (148) decomposed within 24 h at 4°.

Octanal (150)

(i) Jones' oxidation.

By the above method [for the aldehyde (81) part (i)], 348 mg (2.67 mmol) of octanol (BDH) was oxidized to octanoic acid (149) (quantitative). ν_{max} 3000 (v. strong), 1730 cm^{-1} ^1H n.m.r. δ_H0.83, t, 3H; 1.27, bs, 10H; 2.28, t, 2H; 9.7, bs, 1H (exchanged by D_2O).

(ii) *tert*-Butyl chromate oxidation.

By the above method [for the aldehyde (81) part (vi)] 0.50 g (3.85 mmol) of octanol was oxidized to 0.28 g (57%) of octanal (150). The reaction was quenched with dimethyl sulphide[117]. ν_{max} 2700, 1725 cm^{-1}.

(iii) Pyridinium chlorochromate on alumina oxidation.

By the above method [for the aldehyde (81) part (iiib)] 0.40 g (3.08 mmol) of octanol was oxidized to octanal (150) (50% conversion but a quantitative recovery was achieved) over 0.5 h. ν_{max} 3400, 2700 1725 cm^{-1}.

(iv) Dimethylsulphoxide/oxalyl chloride oxidation.

By the above method [for the aldehyde (81) part (xi)], 0.50 g (3.85 mmol) of octanol was oxidized to 0.44 g (90%) of pure octanol (150). ν_{max} 2720, 1730 cm^{-1}. ^1H n.m.r. δ_H 0.9, t, 3H; 1.3, bs, 10H; 2.4, bt, 2H; 9.7, t(J=1.8 Hz), 1H.

N-(3-Hydroxypropyl)-3,3-dimethylacrylamide (139)

This amide was prepared from 3-aminopropanol (Ajax) by the same method and work up as for N-(2-hydroxyethyl)-3,3-dimethylacrylamide (146) (80%), b.p. 100-105° (0.003 mm). (Found: M^+, 157.1112. $C_8H_{15}NO_2$ requires 157.1103). ν_{max} 3300, 2950, 1665, 1545 cm^{-1}. λ_{max} (C_2H_5OH) 218 nm (ε 17000). ^1H n.m.r. δ_H1.70, m, 2H; 1.83, s, 3H; 2.10, s, 3H; 3.37, t, 2H; 3.5, s, 1H (exchanged by D_2O), 3.12, t, 2H; 5.68, s, 1H; 5.8, bs, 1H (exchanged by D_2O). ^{13}C n.m.r. δ_C19.8, 27.1, 32.3, 35.9, 59.2, 118.5, 150.8, 168.4.

Some preparations of the amide (139) yielded varying amounts of ester with the amide (ν_{max} 1720 cm^{-1}. ^1H n.m.r. δ_H4.1) [*vide supra*; amide (146)]. The ester was hydrolysed by heating the crude product at reflux for 4 min in methanolic sodium hydroxide. (For 10 g of crude product, 9 g of sodium hydroxide dissolved in 100 ml of methanol was used). A precipitate that formed was removed by filtration and the alcohol (139) was recovered from the filtrate by evaporation at room temperature followed by the usual work up.

Octadecanoyl chloride (157)

This compound was prepared from octadecanoic acid (stearic acid) by the method described for dodecanoyl chloride (113), b.p. 209-220° (18 mm) [lit.b.p. 215° (18 mm)][111].

Z-9-Octadecenoyl chloride (158)

This compound was prepared from Z-9-octadecenoic acid (oleic acid) by the method described for dodecanoyl chloride (113), b.p. 215-220° (20 mm) [lit. b.p. 213° (13-15 mm)] [104].

4-Chlorobutanol (85)

This compound was prepared according to the method of Starr and Hixon[91], however the same yield required about twice the cited reaction time, b.p. 60-70° (5 mm) [lit. b.p. 65-75° (8 mm)]. ^{1}H n.m.r. δ_H1.8, m, 4H, 3.6, m, 4H; 4.0, s, 1H (exchanged by D_2O).

4-Phthalimidobutanol (162)

This compound was prepared according to the method of Sugiura *et al.*[92]. The product mixture was warmed at 40° for extended periods at 1 mm pressure to remove the dimethylformamide before the product would solidify. Unreacted potassium phthalimide (m.p. > 300°) was removed by slow precipitation from a chloroform solution. 4-Phthalimidobutanol was crystallized from a concentrated solution of the filtrate (37%); m.p. 44-46° (lit. m.p.

57-59°). ^{1}H n.m.r. δ_H1.7, m, 4H; 3.7, m, 5H (1H exchanged by D_2O); 7.65, s, 4H.

N-(4-Bromobutyl)phthalimide (163)

This compound was prepared from 1,4-dibromobutane (Koch-Light) based on the method of Salzburg and Supniewski[50]. (63%), m.p. (cyclohexane) 73-74° (lit. m.p. 79.5-80°[95]). ν_{max} 1770, 1720, 1460, 720 cm^{-1}. ^{1}H n.m.r. δ1.87, m, 4H; 3.45, t, 2H; 3.70, t, 2H; 7.77, s, 4H.

4-Aminobutanol (159)

(i) This amine was prepared by hydrolysis of the imide (87) or the imide (88) with potassium hydroxide according to the method of Puthoken[93], but the yield was only 7% in each case.

(ii) The hydrochloride of the amine (159) was prepared from the alcohol (162) according to the method of Sheehan and Bolhofer[94] in high yield (95%). The free amine was prepared by distillation over crushed potassium hydroxide pellets[93] but was observed to form an azeotrope with water. The amine was distilled twice more after standing between distillations for 72 h over potassium hydroxide pellets. Azeotropic distillation with benzene was unsuccessful in drying the amine (159). Yield of pure aminobutanol was 10%, b.p. 150-170° (lit. b.p. 185-186°)[93]. ^{1}H n.m.r. δ_H1.6, m, 4H; 2.6, bt, 2H; 3.0, bs, 3H (exchanged by D_2O).

4-Aminobutanol (159) was observed to be extremely hygroscopic and in the presence of a trace of water was immiscible with chloroform.

N-(4-Hydroxybutyl)-3,3-dimethylacrylamide (164)

When the acylation was attempted by the usual method in chloroform [*vide supra*: the preparation of amide (146)] a nearly quantitative yield of the amido-ester was formed (t.l.c. and ν_{max} 1730 cm^{-1}). Quantitative recovery of the amido-ester also occurred when dimethylformamide was used as solvent, but when acetonitrile was used as a solvent the amide (164) was isolated in satisfactory yield (58%). The oil was purified by passage down a silica gel column (5% methanol/chloroform), b.p. 114-119° (0.05 mm). (Found: C, 60.2; H, 10.6; N, 7.5. $C_9H_{17}NO_2.\frac{1}{2}H_2O$ requires C, 60.0; H, 10.1; N, 7.8%). (Found: M^+, 171.1278. $C_9H_{17}NO_2$ requires 171.1259). ν_{max} 3300 , 2950, 1670, 1630, 1540 cm^{-1}. ^1H n.m.r. δ_H 1.6, m, 4H; 1.8, s, 3H; 2.1, s, 3H; 3.0-3.7, m, 5H; 5.6, s, 1H; 6.4, bs, 1H. ^{13}C n.m.r. δ_H 19.5, 26.0, 26.9, 38.8, 61.7, 118.5, 150.0, 167.5.

Attempted Preparation of N-(4-Oxobutyl)-3,3-dimethylacrylamide (173)

(i) Jones' oxidation.

By the above method [for the aldehyde (148) part (i)], 21 mg of the amide (164) was oxidized to yield 12 mg of a non-polar product which was not identified. ν_{max} 2950, 1735, 1670, 1630 cm^{-1}. ^1H n.m.r. δ_H 1.2, s; 2.0, s; 2.1, s; 2.6, m;

3.8, t; 6.9, bs.

(ii) Dimethylsulphoxide/oxalyl chloride oxidation.

By the above method [for the aldehyde (148) part (xi)], the amide (164) was oxidized to yield an oil containing about 10% of the aldehyde (173). ν_{max} 3350, 2720 (v. weak), 1720 (v. weak), 1670, 1630, 1550 cm^{-1}. ^1H n.m.r. δ9.54 (the integral was about 10% of the expected integral when compared to the other peaks in the spectrum).

1,5-Diphthalimidopentane (168)

To a solution of 166.3 g (0.506 mole) of 1,5-dibromopentane (Koch-Light) in 1.3 l of dimethylformamide was added 281 g (1.06 mole) of potassium phthalimide (89)[94]. The mixture was heated to 85-110° for 5 h with mechanical stirring, then stood at room temperature overnight. The dimethylformamide was removed by distillation (20 mm). Water (600 ml) was added to the residue and the suspension was heated over a steam bath for 3 h. The residue was isolated from the hot solution by filtration, washed with 200 ml of water and air dried, then heated at reflux in 300 ml of carbon disulphide for 0.5 h. The residue was isolated by filtration, washed with carbon disulphide then left to air dry (261.5 g, quantitative), m.p. 186.5-187.5° (lit. m.p. 188°)[118]. ^1H n.m.r. δ1.74, m, 6H; 3.65, bt, 4H; 7.65, d, 8H.

1,5-Diaminopentane (160)

The preparation of 1,5-diaminopentane (160) was based on the method of Sheehan and Bolhofer[94].

To 262 g (0.72 mole) of diphthalimidopentane (168) in 1.2 l of ethanol was slowly added 113.2 g (2.26 mole) of hydrazine hydrate with swirling. The flask was heated to reflux temperature whereupon a white, voluminous, impenetrable precipitate formed. The mass was partially broken with a glass rod and heating at reflux was continued for 1 h, then cooled. Water (600 ml) was added to the mixture which dissolved the precipitate and the ethanol was removed by distillation. A fine grey suspension (0.5 g) was removed by filtration, then 450 ml of concentrated hydrochloric acid was added to the aqueous solution, causing a precipitate to form, followed by heating over steam with occasional stirring for another 2.5 h. The solution was left overnight then cooled to 0° before removal of the phthalhydrazide by filtration. The filtrate was concentrated to near dryness and another 600 ml of water was added, then distilled to dryness, to remove any residual hydrochloric acid to afford 112.7 g of 1,5-diaminopentane dihydrochloride (160.2 HCl) (89%), m.p. 257° (lit. m.p. 255°)[119], m.p. (picrate) 223-224°(dec.) (lit. m.p. 225-230°)[120]. The free diamine (160) was obtained by distillation from a mixture of sodium hydroxide crushed with soda-lime followed by distillation from potassium hydroxide (70%)[93]. The diamine (160) was stored over potassium hydroxide pellets, b.p. 175-180° (lit. 178-180°)[93].

N-(2,2-Dimethoxyethyl)-3,3-dimethylacrylamide (166)

This amide was prepared from aminoacetaldehyde dimethylacetal (167) (Aldrich) by the same method as for N-(2-hydroxyethyl)-3,3-dimethylacrylamide (146) and worked up in the usual manner (95%), b.p. 65-70° (0.004 mm). (Found: C, 55.4; H, 9.4; N, 7.3. $C_9H_{17}NO_3.\frac{1}{2}H_2O$ requires C, 55.1; H, 9.3; N, 7.1%). (Found: M^+, 187.1203. $C_9H_{17}NO_3$ requires 187.1208). ν_{max} 3300, 2950, 2810, 1660, 1635, 1125, 1100, 1060 cm^{-1}. ^1H n.m.r. δ_H1.50, s, 3H; 2.17; s, 3H; 3.38, d over s, 8H; 4.41, t, 1H; 5.65, s, 1H; 6.43, bt, 1H (exchanged by D_2O). ^{13}C n.m.r δ_C19.7, 27.1, 40.7, 54.1, 102.9, 118.6, 150.7, 167.3.

N-(5-Hydroxypentyl)-3,3-dimethylacrylamide (165)

This amide was prepared from 5-aminopentanol (Aldrich) by the above method and worked up in the usual manner (88%), b.p. 120-129° (0.004 mm). (Found: C, 63.3; H, 10.8; N, 7.1. $C_{10}H_{19}NO_2.\frac{1}{4}H_2O$ requires C, 63.3; H, 10.4; N, 7.6%). (Found: M^+, 185.1395. $C_{10}H_{19}NO_2$ requires 185.1415). ν_{max} 3350, 2950, 1670, 1630, 1550 cm^{-1}. ^1H n.m.r. δ_H1.45, bs, 6H; 1.82, s, 3H; 2.10, s, 3H; 2.9-3.3, m, 3H; 3.60, t, 2H; 5.55, s, 1H; 6.05, bs, 1H. ^{13}C n.m.r. δ_C19.5, 23.0, 26.9, 29.1, 32.0, 38.9, 61.9, 118.5, 150.0, 167.3.

N-(*tert*-Butyloxycarbonyl)-1,5-diaminopentane (169)

This carbamate was prepared by the method described for N-(*tert*-butyloxycarbonyl)-1,6-diaminohexane (131) but recrystallized from a mixture of ethanol and ether (1:10)

(49%) m.p. 112-113°. (Found: C, 50.2; H, 9.9; N, 12.0. $C_{10}H_{23}ClN_2O_2$ requires C, 50.3; H, 9.7; N, 11.7%). ν_{max} 1690 cm^{-1}. ^1H n.m.r. δ_H1.43, bs, 15H; 4.72, bt, 4H; 5.1, broad, 1H (exchanged by D_2O); 7.77, s, 3H (exchanged by D_2O). ^{13}C n.m.r. δ_C23.6, 26.8, 28.5, 29.2, 39.7, 40.3, 79.2, 156.8.

N-(*tert*-Butyloxycarbonyl)-1,4-diaminobutane(170)

This carbamate was prepared by the above method from 1,4-diaminobutane (Aldrich). The salt (170.HCl) did not precipitate from the saturated sodium chloride solution, therefore it was isolated by extraction with 5% 2-propanol/chloroform and recrystallized from 2-propanol/ether (65%), m.p. 157°. (Found: C, 47.9; H, 9.8; N, 12.7. $C_9H_{21}ClN_2O_2$ requires C, 48.1; H, 9.4; N, 12.5%). ν_{max} 3350, 2950, 2750, 2640, 2540, 2000, 1695 cm^{-1}. ^1H n.m.r. δ_H1.4, s, 9H; 3.10, bt, 4H; 5.32, bs, 1H (exchanged by D_2O); 7.4-8.6, bs, 2H (exchanged by D_2O). ^{13}C n.m.r. $\delta(D_2O)$ 24.9, 26.9, 28.6, 40.0, 81.6, 158.9.

N-(*tert*-Butyloxycarbonyl)-1,2-diaminoethane (171)

This carbamate was prepared and worked up by the above method (38%), m.p. 153.5-154°. (Found: M^+ (free amine), 160.1172. $C_7H_{16}N_2O_2$ requires 160.1212). ν_{max} 3350, 2950, 2750-2450 (7 peaks), 2050, 1695 cm^{-1}. ^1H n.m.r. $\delta_H(D_2O)$ 1.52, s, 9H; 3.20, m, 2H; 3.42, m. 2H. ^{13}C n.m.r. (acetone-d_6) δ_C 28.5, 38.5, 40.3, 80.4, 157.8.

Attempted Preparation of N-[9-(*tert*-Butyloxycarbonylamino)-hexyl]iminoethyl-3,3-dimethylacrylamide (172)

(i) To a suspension of 210 mg (0.83 mmol) of the amine (131), 115 mg (0.83 mmol) of potassium carbonate and 0.5 g of molecular sieves (4Å) in 4 ml of dichloromethane was added 63 mg (0.83 mmol) of the acetal (166). The stirred suspension was monitored by ^{1}H n.m.r. No reaction was observed after 2 days.

(ii) The above reaction was repeated, except the compounds were heated at reflux in chloroform. The solution slowly went black with no appearance of the imine proton (^{1}H n.m.r.).

(iii) The above reaction was repeated, except that triethylamine replaced the potassium carbonate. Stirring at room temperature and heating at reflux were unsuccessful, according to ^{1}H n.m.r.

(iv) The amine free-base (131) was prepared by extraction with chloroform from 10% sodium hydroxide in the usual manner. The amine (131) and the acetal (166) were mixed without solvent and heated over steam ($\simeq$ 80%). No reaction occurred (^{1}H n.m.r.) so one drop of acetic acid was added. No reaction was observed after standing at room temperature for 3 days, nor after being heated over steam for 24 h.

N-(3-Oxopropyl)-3,3-dimethylacrylamide (151)

(i) This aldehyde was prepared according to the method of Swern *et al.*[87] [*vide supra*, for the aldehyde (148) part (xi) and for octanal (150) part (iv)]. The largest scale was 8.96 g (57.1 mmol) of alcohol (139) oxidised to afford the aldehyde (151) (6.89 g, 78%). (Found: M^+, 155.0925. $C_8H_{13}NO_2$ requires 155.0946). ν_{max} 3350, 2740, 1725, 1675 cm^{-1}. ^1H n.m.r. δ_H1.83, s, 3H; 2.12, s, 3H; 2.72, t, 2H; 3.51, m, 2H; 5.57, s, 1H; 6.53, bs, 1H (exchanged by D_2O); 9.72, s, 1H. A reduction in the formyl proton peak area occurred after storage for 18h at 4°. ^{13}C n.m.r. δ_C19.7, 27.1, 32.8, 44.0, 118.5, 150.8, 167.4, 201.7.

The aldehyde (151) was normally used immediately without further purification, but chromatography on silica gel (chloroform) increased the stability of the aldehyde.

(ii) Oxidation of the alcohol (139) was attempted using *tert*-butyl chromate according to the method of Sharpless *et al.*[82] [*vide supra*, for the aldehyde (148) part (vi) and octanal (150) part (ii)]. Recovery was only 10%. ν_{max} 3350 (v. strong), 1730 cm^{-1}.

N-(5-Oxopentyl)-3,3-dimethylacrylamide (173)

This unstable aldehyde was prepared by the above method (Swern) (94%). ν_{max} 3300, 2950, 2720, 1720, 1670, 1630 cm^{-1}. ^1H n.m.r. δ_H1.60, m, 4H; 1.85, s, 3H; 2.10, s, 3H; 2.40, bt, 2H; 3.3, bt, 2H; 5.56, s, 1H; 6.1, bs, 1H; 9.72, s, 1H.

N-(2-Oxoethyl)-3,3-dimethylacrylamide (148)

To 5.36 g (28.7 mmol) of the acetal (166) was added a solution of 15 ml of 10M hydrochloric acid (Ajax, AR) in 135 ml of water. The solution was stirred at room temperature for 50 min then neutralised (pH paper) with solid sodium bicarbonate. The solution was saturated with sodium chloride and chloroform extraction afforded 4.00 g (99%) of the unstable aldehyde (148) in admixture with a small amount of unreacted acetal (166) (^1H n.m.r.). (Found: M^+, 141.0789. $C_7H_{11}NO_2$ requires 141.0789). ^1H n.m.r. δ_H1.82, s, 3H; 2.08, s, 3H; 3.36, bs, 2H, 5.61, s, 1H; 6.3, bs, 1H; 9.57, s, 1H. ^{13}C n.m.r. δ_C19.9, 27.2, 50.0, 117.5, 152.8, 167.3, 197.6.

Hydrolysis of the acetal (166) was attempted in saturated tartaric acid solution according to the method of Hurd *et al.*[96] (followed by the usual work up), but without success. The hydrolyses were monitored by t.l.c.

(i) After stirring at room temperature for 1 h only one product was detected (loss of starting acetal complete). ν_{max} 3350, 1730 cm^{-1}.

(ii) After heating over steam for 1 min, one product formed. ν_{max} 3350, 2720 (v. weak), 1730 (v. weak), 1675 cm^{-1}. Further heating produced two products.

Secondary Amines

The secondary amines (152 and 152-181) were prepared from the requisite aldehydes and carbamates according to the following standard procedure.

N-(*tert*-Butyloxycarbonyl)-N'-[3-(3,3-dimethylacrylamido)-propyl]-1,6-diaminohexane (152)

The aminium chloride (131.HCl) (4.85 g, 19.3 mmol) was dissolved in 15 ml of 19% aqueous sodium hydroxide. Brine (5 ml) was added and the solution was worked up with chloroform (3 x 10 ml) to give the amine (131) which was then dissolved in 60 ml of chloroform to which 1 g of 4Å molecular sieves had been added. The freshly prepared aldehyde (151) (3.50 g, 22.6 mmol) in 100 ml of chloroform was added in one aliquot, and the solution was stirred for 1.2 h or until the formyl proton could no longer be observed (^1H n.m.r.). The solution was filtered and evaporated to an oil, then redissolved in 15 ml of ethanol. Sodium borohydride (858 mg, 22.6 mmol) dissolved in 20 ml of ethanol, was added immediately and the effervescent solution was stirred at room temperature for 30 min or heated at reflux for 20 min. The ethanol was removed under reduced pressure and the oil was acidified with 1% hydrochloric acid and extracted with ethyl acetate

(3 x 20 ml). The aqueous phase was saturated with solid sodium chloride then extracted with 5% 2-propanol/ chloroform (3 x 20 ml), dried over sodium sulphate and evaporated to give the secondary amine (152) (5.34 g, 72%), m.p. (2-propanol/ether) 106.5-107.0°. (Found: C, 56.9; H, 9.8. $C_{19}H_{38}ClN_3O_3.\frac{1}{2}H_2O$ requires C, 56.9; H, 10.1%). ν_{max} 3350, 2420, 1675, 1640 cm^{-1}. ^1H n.m.r. δ_H1.45, s, 19H; 1.87, s, 3H; 2.14, s, 3H; 2.6-3.5, m (broad), 8H; 4.98, bs, 1H (exchanged by D_2O); 5.78, s, 1H; 7.82, bs, 1H (exchanged by D_2O); 9.40, bs, 2H (exchanged by D_2O). ^{13}C n.m.r. δ_C20.0, 26.1, 26.3, 27.4, 28.5, 29.8, 35.6, 40.5, 45.5, 48.3, 78.8, 118.3, 151.8, 156.3, 168.9. When this reaction was repeated using ethanol instead of chloroform (as a "one-pot" synthesis) a lower yield was achieved (20%).

N-(*tert*-Butyloxycarbonyl)-N'[3-(3,3-dimethylacrylamido)-propyl]-1,5-diaminopentane (175)

This amine was prepared by the above procedure (71%), m.p. (2-propanol/ether) 85-86°. (Found: C, 56.9; H, 9.3; N, 11.4. $C_{18}H_{36}ClN_3O_3$ requires C, 57.2; H, 9.6; N, 11.1%). (Found: M^+ (free amine), 341.2683. $C_{18}H_{35}N_3O_3$ requires 341.2678). ν_{max} 3350, 2420, 1690, 1675, 1640 cm^{-1}. ^1H n.m.r. δ_H1.45, s, 17H; 1.87, s, 3H; 2.14, s, 3H; 2.6-3.5, m (broad), 8H; 4.98; bs, 1H (exchanged by D_2O); 5.78, s, 1H; 7.82, bs, 1H (exchanged by D_2O); 9.4, bs, 2H (exchanged by D_2O). ^{13}C n.m.r. δ_C19.5, 24.3, 26.9, 28.2, 28.9, 29.6, 29.7, 37.5, 40.2, 47.5, 49.3, 78.8, 118.6, 149.7, 156.1, 168.8

N-(*tert*-Butyloxycarbonyl)-N'-[3-(3,3-dimethylacrylamido)-propyl]-1,4-diaminobutane (176)

This amine was prepared by the above procedure except that the imine was prepared at 0° using solutions precooled over ice (79%), m.p. (ethyl acetate/ether) 116.0-116.5°. (Found: C, 54.9; H, 10.1; N, 11.1. $C_{17}H_{34}CLN_3O_3.\frac{1}{2}H_2O$ requires C, 54.7; H, 9.5; N, 11.3%). ν_{max} 3350, 2420, 1690, 1670, 1630 cm^{-1}. ^1H n.m.r. δ_H1.40, s, 9H; 1.6-1.9, bs, 6H; 2.13, s, 3H; 2.65-3.55, m, 8H; 5.25, s, 1H (exchanged by D_2O); 5.70, s, 1H; 7.7, bs, 1H (exchanged by D_2O); 9.4, bs, 2H (exchanged by D_2O). ^{13}C n.m.r. δ_C19.6, 23.0, 26.2, 26.7, 27.0, 28.1, 35.1, 39.5, 44.9, 47.5, 78.9, 117.8, 151.7, 156.0, 168.6.

When this and the following preparations of the secondary amines were attempted at room temperature many products were formed and the yield of the appropriate secondary amine dropped to <5%.

pH Profile

The compound (176) was dissolved in water and the pH adjusted with 1% hydrochloric acid or 0.5M potassium hydroxide. The pH measurements were carried out with a "Radiometer" pH meter Model 23, fitted with a "Metrohm" AG 9100 combined electrode assembly. At high pH (>10.5) the compound partially oiled out of solution. Only the "spermidine" [cf. (27)] carbons were measured.

^{13}C n.m.r. δ_C(pH 7.3) 20.3, 23.8, 26.7, 27.0, 27.1, 28.6, 36.7, 40.4, 46.0, 48.3. (pH 8.2) 20.3, 23.9, 26.8,

27.1, 28.6, 36.7, 40.4, 46.0, 48.3. (pH 8.8) 20.3, 24.1, 27.0, 27.1, 28.6, 36.8, 40.5, 46.1, 48.4. (pH 9.6) 20.3, 24.9, 27.1, 27.3, 27.7, 28.6, 37.1, 40.6, 46.3, 48.6. (pH 10.0) 20.2, 25.5, 27.0, 27.4, 28.2, 28.6, 37.5, 40.8, 46.5, 48.8. (pH 10.7) 26.2, 26.9, 27.6, 28.6, 28.8, 37.8, 40.9, 46.8, 48.9. (pH 11.9) 26.6, 26.9, 27.7, 28.6, 29.1, 38.0, 41.0, 46.8, 49.1.

N-(*tert*-Butyloxycarbonyl)-N'-[3-(3,3-dimethylacrylamido)-propyl]-1,2-diaminoethane (177)

This amine was prepared by the above procedure (80%) m.p. (ethylacetate/ether) 126.5-127.0°. (Found: C, 52.9; H, 9.3; N, 12.5. $C_{15}H_{30}ClN_3O_3.\frac{1}{4}H_2O$ requires C, 52.9; H, 9.0; N, 12.4%). ν_{max} 3390, 3330, 2950, 2800-2450 (4 peaks), 1700, 1670, 1630 cm^{-1}. ^1H n.m.r. δ_H1.40, s, 9H; 1.80, s, 3H; 1.9-2.2, m, 2H; 2.18, s, 3H; 3.1, m, 4H; 3.5, m. 4H, 5.65, s, 1H; 6.20, bs, 1H (exchanged by D_2O); 7.85, bs 1H (exchanged by D_2O); 9.4, bs, 2H (exchanged by D_2O). ^{13}C n.m.r. δ_C20.0, 26.6, 27.3, 28.4, 35.3, 37.3, 45.4, 48.6, 79.9, 118.0, 152.1, 156.4, 169.0.

N-(*tert*-Butyloxycarbonyl)-N'-[5-(3,3-dimethylacrylamido)-pentyl]-1,5-diaminopentane (178)

This amine was prepared by the above procedure (63%). The amine could not be isolated pure by repeated recrystallization from several different solvents, m.p. 118-119. ν_{max} 3350, 1700, 1670, 1640 cm^{-1}. ^1H n.m.r. δ_H 1.48, bs, 21H; 1.80, s, 3H; 2.10, s, 3H; 2.6-3.7, m,

8H; 5.05, bs, 1H (exchanged by D_2O); 5.65, s, 1H; 5.80, s, 1H (exchanged by D_2O); 8.0-9.3, bd, 2H (exchanged by D_2O). ^{13}C n.m.r. δ_C20.0, 23.2, 23.9, 25.5, 27.2, 28.5, 29.3, 32.1, 39.2, 40.4, 47.0, 48.0, 79.3, 118.4, 156.4, 168.1.

N-(*tert*-Butyloxycarbonyl)-N'-[5-(3,3-dimethylacrylamido)-pentyl]-1,2-diaminoethane (179)

This amine was prepared by the above procedure (50%), m.p. (ethyl acetate/ether) 143.0-143.5°. (Found: C, 55.9; H, 9.7; N, 11.3. $C_{17}H_{34}ClN_3O_3$ requires C, 56.1; H, 9.4; N, 11.6%). ν_{max} 3350, 2950, 1690, 1665, 1630 cm^{-1}. ^1H n.m.r. δ_H1.4, bs, 15H; 1.82, s, 3H; 2.09, s, 3H; 2.7-3.7, m, 8H; 4.85, bs, 1H (exchanged by D_2O); 5.72, s, 1H; 6.25, bs, 1H (exchanged by D_2O); 9.22, bs, 2H (exchanged by D_2O). ^{13}C n.m.r. δ_C19.7, 23.6, 25.3, 27.0, 28.2, 28.4, 37.1, 38.6, 47.9, 48.2, 79.8, 118.4, 150.5, 156.3, 167.7.

N-(*tert*-Butyloxycarbonyl)-N'-[2-(3,3-dimethylacrylamido)-ethyl]-1,5-diaminopentane (180)

This amine was prepared by the above procedure (70%), m.p. (2-propanol/ether) 128-129°. (Found: C, 55.8; H, 9.4; N, 11.7. $C_{17}H_{34}ClN_3O_3$ requires C, 56.1; H, 9.4; N, 11.6%). ν_{max} 3370, 3330, 2700, 1690, 1630 cm^{-1}. ^1H n.m.r. δ_H1.45, bs, 15H; 1.84, bs, 5H; 2.15, s, 3H; 3.10, m, 6H; 3.65, m. 2H; 5.10, bs, 1H (exchanged by D_2O); 5.65, s, 1H; 7.95, bs, 1H (exchanged by D_2O); 9.25, bs, 2H (exchanged by D_2O). ^{13}C n.m.r. δ_C 19.5, 23.3, 25.3, 26.9,

28.1, 28.9, 35.7, 39.8, 47.7, 48.0, 78.7, 117.7, 152.0, 156.0, 168.1.

N-(*tert*-Butyloxycarbonyl)-N'-[2-(3,3-dimethylacrylamido)-ethyl]-1,2-diaminoethane (181)

This amine was prepared by the above procedure (50%) m.p. 156.5-157.0°. (Found: C, 51.8; H, 9.1; N, 13.2. $C_{14}H_{28}ClN_3O_3$ requires C, 52.2; H, 8.8; N, 13.1%). ν_{max} 3350, 2950, 2750 (multiplet), 2450, 1700, 1630 cm^{-1}. ^1H n.m.r. δ_H1.40, s, 9H; 1.82, s, 3H; 2.10, s, 3H; 3.18, bs, 4H; 3.6, bs, 4H; 5.65, s, 1H; 6.05, bs, 1H (exchanged by D_2O), 7.69, bs, 1H (exchanged by D_2O); 7.82, bs, 2H (exchanged by D_2O). ^{13}C n.m.r. δ_C20.0, 27.3, 28.4, 29.7, 36.2, 37.5, 48.5, 80.1, 118.1, 152.4, 156.4, 168.4.

N,N-Disubstituted Amides

The N,N-disubstituted amides (153 and 182-198) were prepared from the requisite acyl chlorides and secondary amines according to the following standard procedure. The amides [except for (233) and (234)] pyrolized (loss of ν_{max} 1710 cm^{-1}) upon attempted distillation at *ca.* 0.004 mm (b.p.>230°). They could not be purified by h.p.l.c. (cyanopropylsilane column).

All chemical ionization mass spectrometric samples were introduced by direct probe and analyses were undertaken with isobutane gas unless otherwise mentioned.

N-[6-(*tert*-Butyloxycarbonylamino)hexyl]-N-[3-(3,3-dimethylacrylamido)propyl]dodecanamide (153)

To an ice cold, stirred solution of 1.16 g (2.95 mmol) of the secondary amine and 0.75 g (7.5 mmol) of triethylamine, in 40 ml of dichloromethane, was slowly added 0.71 g (3.23 mmol) of dodecanoyl chloride (113) dissolved in 15 ml of dichloromethane. The reaction was allowed to warm to room temperature after all the acyl chloride (113) had been added and stirred for another 3 h (or overnight) before it was worked up with chloroform. Chromatography on silica gel (2% methanol/ether) afforded 1.15 g (73%) of the amide (153). (Found: (h.r.f.a.b.) MNa^+, 560.4427. $C_{31}H_{59}N_3O_4Na$ requires 560.4403). ν_{max} 3300, 1710, 1680, 1630 cm^{-1}. ^1H n.m.r. δ_H0.87, t, 3H; 1.27, s, 20H; 1.43, s, 9H; 1.62, m. 8H; 1.82, s, 3H; 2.13, s, 3H; 2.32, t, 2H; 3.22, m (broad), 8H; 4.70, bs, 1H; 5.60, s, 1H; 6.72, bs, 1H. ^{13}C n.m.r. δ_C13.9, 19.4, 22.5, 25.5, 26.3, 26.8, 28.2, 29.1, 29.3, 29.4, 29.8, 31.7, 32.9, 35.1, 40.2, 42.0, 45.5, 47.5, 78.8, 119.0, 149.5, 155.9, 166.9, 173.7.

N-[6-(*tert*-Butyloxycarbonylamino)hexyl]-N-[3-(3,3-dimethylacrylamido)propyl]octadecanamide (182)

This amide was prepared by the above procedure and chromatographed on silica gel (1% methanol in chloroform) (91%). ν_{max} 3300, 1720, 1660, 1630 cm^{-1}. ^1H n.m.r. δ_H0.87, t, 3H; 1.26, s, 30H; 1.42, s, 11H; 1.62, m, 8H; 1.81, s, 3H; 2.10, s, 3H; 2.29, t, 2H; 3.25, m, 8H;

4.70, bs, 1H; 5.60, s, 1H; 6.80, bs, 1H. ^{13}C n.m.r. δ_C13.9, 19.5, 22.4, 25.5, 26.3, 26.8, 27.2, 28.2, 28.8, 29.1, 29.5, 29.8, 31.7, 32.9, 35.1, 40.4, 40.5, 42.1, 47.6, 78.9, 118.9, 149.6, 167.2, 173.8, 193.6. Mass spectrum (c.i.) m/z 622 (MH^+).

N-[6-(*tert*-Butyloxycarbonylamino)hexyl]-N-[3-(3,3-dimethylacrylamido)propyl]octadec-9-enamide (183)

This amide was prepared by the above procedure and chromatographed on silica gel (chloroform) (88%). ν_{max} 3300, 1700, 1670, 1630 cm^{-1}. ^1H n.m.r. δ_H0.85, t, 3H; 1.28, s, 24H; 1.42, s, 11H; 1.65, m, 8H; 1.80, s, 3H; 2.0, m, 6H; 2.19, s, 3H; 2.26, t, 2H; 3.22, m, 8H; 4.70, bs, 1H; 5.31, t, 2H; 5.60, s, 1H; 6.8, bs, 1H. ^{13}C n.m.r. δ_C14.1, 16.7, 22.7, 24.1, 25.7, 26.1, 27.1, 27.2, 27.5, 28.4, 29.2, 29.3, 29.5, 29.7, 29.9, 31.9, 33.2, 35.3, 40.3, 42.4, 47.6, 79.4, 119.1, 129.7, 139.9, 150.1, 156.2, 167.2, 173.9. Mass spectrum (c.i.) m/z 620 (MH^+), 546 ($MH^+-C_4H_{10}O$); (MH^+), 520 ($MH^+ -CO_2-C_4H_8$).

N-[5-(*tert*-Butyloxycarbonylamino)pentyl]-N-[3-(3,3-dimethylacrylamido)propyl]acetamide (184)

This amide was prepared by the above procedure and chromatographed on silica gel (3% methanol/chloroform) (76%). ν_{max} 3350, 1700, 1670, 1635 cm^{-1}. ^1H n.m.r. δ_H 1.46, bs, 11H; 1.5-1.8, m, 6H; 1.85, s, 3H; 1.92, s, 3H; 2.18, s, 3H; 3.25,m (broad) 8H, 4.8, bs, 1H; 5.60, s, 1H; 6.7, bs, 1H. ^{13}C n.m.r. δ_C19.4, 21.1, 23.7, 26.8, 27.2, 28.2, 29.6, 35.1,

40.0, 42.0, 48.3, 78.8, 118.9, 149.5, 155.9, 166.9, 170.9. Mass spectrum (c.i.) m/z 384 (MH^+), 328, 310, 284.

N-[5-(*tert*-Butyloxycarbonylamino(pentyl]-N-[3-(3,3-dimethyl-acrylamido)propyl]dodecanamide (185)

This amide was prepared by the above procedure and chromatographed on silica gel (1.5% methanol/chloroform) (90%). Purification for micro analysis was by exhaustive h.p.l.c. (cyanopropylsilane column, 15% heptane/dichloromethane. (Found: C, 68.6; H, 11.5; N, 7.7. $C_{30}H_{57}N_3O_4$ requires C, 68.8; H, 11.0; N, 8.0%. (Found: (h.r.f.a.b)MNa^+, 546.4248. $C_{30}H_{57}N_3O_4Na$ requires 546.4247). ν_{max} 3350, 2900, 1710, 1630 cm^{-1}. ^1H n.m.r. δ_H0.87, b, 3H; 1.28, s, 18H; 1.43, s, 9H; 1.62, m, 8H; 1.82, s, 3H; 2.14, s, 3H; 2.32, t, 2H; 3.23, m (broad), 8H; 4.70, bs, 1H; 5.60, s, 1H; 6.73, bs, 1H. ^{13}C n.m.r. δ_C 14.1, 22.6, 24.1, 25.7, 27.1, 28.4, 29.3, 29.5, 29.9, 31.9, 33.2, 35.2, 40.3, 42.2, 47.7, 119.0, 149.7, 156.0, 167.0, 173.9. Mass spectra (f.a.b.) m/z 524 [10%, MH^+. (The addition of Na^+ formed MNa^+ 1.5 times larger than MH^+)], 467 (5,M-C_4H_8), 450 (7, M-$C_4H_{10}O$), 424 (100, M-CO_2-C_4H_8), 369 (18, M-$C_{11}H_{23}$), 140 (38), 83 (82, C_5H_7O). C.i. m/z 524, 468, 450, 424. C.i. (ammonia) m/z 524, 424.

N-[5-(*tert*-Butyloxycarbonylamino)pentyl]-N-[3-(3,3-dimethyl-acrylamido)propyl]octadecanamide (186)

This amide was prepared and purified by the above procedure (92%). ν_{max} 3340, 2950, 1710, 1630 cm^{-1}.

^{1}H n.m.r. δ_H0.88, t, 3H, 1.25, s, 28H; 1.43, s, 11H; 1.62, m, 8H; 1.80, s, 3H; 2.13, s, 3H; 2.28, t, 2H; 3.15, m, 8H; 4.78, bs, 1H; 5.60, s, 1H; 6.78, bs, 1H. ^{13}C n.m.r. δ_C14.0, 19.5, 22.6, 23.9, 25.6, 26.9, 27.3, 28.3, 28.5, 29.2, 29.4, 29.5, 29.8, 31.8, 33.0, 35.1, 40.2, 42.1, 47.6, 119.0, 149.7, 156.0, 167.0, 173.9. Mass spectrum (c.i.) m/z 608 (MH^+), 580 ($MH^+-C_2H_4$), 508 ($MH^+-CO_2-C_4H_8$), 369 ($MH^+-C_{17}H_{35}$).

N-[5-(*tert*-Butyloxycarbonylamino)pentyl]-N-[3-(3,3-dimethyl-acrylamido)propyl]octadec-9-enamide (187)

This amide was prepared and purified by the above procedure (91%). ν_{max} 3340, 2950, 1710, 1630 cm^{-1}. ^{1}H n.m.r. δ_H0.88, t, 3H; 1.25, s, 22H; 1.43, s, 11H; 1.6, m, 8H; 1.80, s, 3H; 2.0, m, 6H; 2.13, s, 3H; 2.28, t, 2H; 3.15, m (broad), 8H; 4.77, bs, 1H; 5.30, t, 2H; 5.60, s, 1H; 6.78, bs, 1H. ^{13}C n.m.r. δ_C14.0, 16.7, 22.7, 24.1, 25.7, 27.1, 27.2, 27.4, 28.4, 29.2, 29.3, 29.5, 29.7, 29.9, 31.9, 33.2, 35.3, 40.3, 42.4, 47.7, 79.4, 119.1, 129.7, 130.0, 150.0, 156.1, 167.2, 174.0. Mass spectrum (c.i.) m/z 606 (MH^+), 550 ($MH^+-C_2H_4$), 532 ($MH^+-C_4H_{10}O$), 506 ($MH^+-CO_2-C_4H_8$), 369 ($MH^+-C_{17}H_{33}$).

N-[4-(*tert*-Butyloxycarbonylamino)butyl]-N-[3-(3,3-dimethyl-acrylamido)propyl]dodecanamide (188)

This amide was prepared by the above procedure (97%). ν_{max} 3350, 2950, 1710, 1630 cm^{-1}. ^{1}H n.mr. δ_H0.89, t, 3H; 1.3, s, 16H; 1.5, s, 9H; 1.6, m, 6H; 1.85, s, 3H; 2.2, s, 3H; 2.3, t, 2H; 3.2, m, 8H; 4.95, bt, 1H; 5.62, s, 1H; 6.82, bt, 1H.

^{13}C n.m.r. δ_C13.8, 19.4, 22.3, 25.4, 25.8, 26.7, 27.3, 28.1, 29.0, 29.2, 31.6, 32.8, 35.1, 39.7, 42.0, 47.2, 78.8, 118.9, 149.4, 155.9, 166.9, 173.6. Mass spectrum (c.i.) m/z 510 (MH^+), 436, 410.

N-[4-(*tert*-Butyloxycarbonylamino)butyl]-N-[3-(3,3-dimethylacrylamido)propyl]octadecanamide (189)

This amide was prepared by the above procedure (97%). ν_{max} 3350, 2930, 1710, 1690, 1630, cm^{-1}. ^1H n.m.r. δ_H 0.89, t, 3H; 1.30, s, 26H; 1.43, s, 11H; 1.5-1.9, m, 8H; 1.85, s, 3H; 2.20, s, 3H; 2.33, t, 2H; 3.15, m. 8H; 4.85, bs, 1H; 5.60, s, 1H; 6.8, bs, 1H. ^{13}C n.m.r. δ_C 13.9, 19.5, 22.5, 25.5, 25.9, 26.8, 27.4, 28.2, 29.2, 29.3, 29.5, 31.7, 33.0, 35.1, 39.7, 39.8, 42.0, 47.2, 79.0, 119.0, 149.6, 173.7. Mass spectrum (c.i.) m/z 594 (MH^+), 566, 520, 494.

N-[4-(*tert*-Butyloxycarbonylamino)butyl]-N-[3-(3,3-dimethylacrylamido)propyl]octadec-9-enamide (190)

This amide was prepared by the above procedure (98%). ν_{max} 3350, 2950, 1705, 1670, 1630 cm^{-1}. ^1H n.m.r. δ_H0.9, t, 3H; 1.30, s, 2H; 1.50, s, 9H; 1.67, m. 6H; 1.80, s, 3H; 1.99, m. 2H; 2.15, s, 3H; 2.30, t, 2H; 3.15, m (broad), 8H; 5.05, bt, 1H; 5.35, t, 2H; 5.61, s, 1H; 6.9, bt, 1H. ^{13}C n.m.r. 13.7, 19.3, 22.3, 25.3, 25.8, 26.7, 26.8, 27.2, 28.1, 28.8, 28.9, 29.1, 29.3, 31.5, 32.7, 35.0, 39.6, 39.7, 42.0, 47.1, 78.6, 118.8, 129.4, 129.6, 155.8, 166.8, 173.5. Mass spectrum (c.i.) m/z 592 (34% MH^+), 518 (100, MH^+-$C_4H_{10}O$), 492 (95, MH^+-CO_2-C_4H_8), 466 (34, MH^+-$Me_2C{=}CHCONHCH_2CH_2$),

369 (53, $MH^+-C_{16}H_{30}$).

N-[2-(*tert*-Butyloxycarbonylamino)ethyl]-N-[3-(3,3-dimethyl-acrylamido)propyl]dodecanamide (191)

This amide was prepared by the above procedure (98%). ν_{max} 3350, 2950, 1710, 1670, 1630 cm^{-1}. ^1H n.m.r. δ_H0.85, t, 3H; 1.2, s, 16H; 1.39, bs, 11H; 1.70, m. 2H; 1.83, s, 3H; 2.11, s, 3H; 2.30, t, 2H; 3.3, m, 8H; 5.1, bs, 1H; 5.60, s, 1H; 6.67, bs, 1H. ^{13}C n.m.r. δ_C14.1, 19.7, 22.7, 25.7, 27.1, 27.5, 28.4, 29.3, 29.5, 29.6, 31.3, 33.1, 33.2, 35.4, 36.5, 39.4, 42.3, 47.0, 80.0, 119.1, 150.0, 156.0, 167.2, 174.6. Mass spectrum (c.i.) m/z 482 (MH^+), 382 ($MH^+-CO_2-C_4H_8$).

N-[2-(*tert*-Butyloxycarbonylamino)ethyl]-N-[3-(3,3-dimethyl-acrylamido)propyl]octadecanamide (192)

This amide was prepared by the above procedure (98%). ν_{max} 3350, 2950, 1715, 1640 cm^{-1}. ^1H n.m.r. δ_C0.85, t, 3H; 1.25, s, 26H; 1.40, s, 9H; 1.65, m. 4H; 1.80, s, 3H; 2.00, m, 2H; 2.15, s, 3H; 2.3, m, 2H; 3.28, m. 8H; 5.0, bs, 1H; 5.58, s, 1H; 6.7, bs, 1H. ^{13}C n.m.r. δ_C14.1, 19.7, 22.7, 25.7, 27.1, 28.4, 29.4, 29.5, 29.7, 31.9, 33.1, 35.4, 42.3, 47.0, 80.0, 119.1, 150.6, 155.8, 167.5, 174.5. Mass spectrum (c.i.) m/z 566 (MH^+, 2%) (many uninterpretable peaks).

N-[2-(*tert*-Butyloxycarbonylamino)ethyl]-N-[3-(3,3-dimethyl-acrylamido)propyl]octadec-9-enamide (193)

This amide was prepared by the above procedure (98%). ν_{max} 3350, 2950, 1710, 1630 cm^{-1}. ^1H n.m.r. δ_H0.85, t, 3H;

1.25, s, 20H; 1.41, s, 9H; 1.6-2.05, m under s, 11H; 2.15, s, 3H; 2.3, m, 2H; 3.3, m, 8H; 5.10, bs, 1H; 5.30, t, 2H; 5.60, s, 1H; 6.7, bs, 1H. ^{13}C n.m.r. δ_C 14.1, 19.7, 22.7, 25.7, 27.1, 27.2, 27.5, 28.4, 29.2, 29.3, 29.5, 29.7, 31.9, 32.6, 33.1, 35.4, 39.3, 42.3, 47.1, 80.0, 119.1, 129.8, 130.0, 150.0, 156.0, 167.2, 174.5. Mass spectrum (c.i.) m/z 564 (MH+), 490, 464.

N-[5-(*tert*-Butyloxycarbonylamino)pentyl]-N-[5-(3,3-dimethylacrylamido)pentyl]dodecanamide (194)

This amide was prepared and purified by the described method (83%). ν_{max} 3340, 2940, 1710, 1630 cm^{-1}. ^{1}H n.m.r. δ_H 0.88, t, 3H; 1.22, s, 22H; 1.45, s, 9H; 1.6, m (broad), 10H; 1.82, s, 3H; 2.15, s, 3H; 2.25, t, 2H; 3.1, m (broad), 8H; 4.75, bs, 1H; 5.60, s, 1H; 6.0, bs, 1H. ^{13}C n.m.r. δ_C 14.1, 19.7, 22.7, 24.1, 25.6, 27.1, 28.4, 28.9, 29.3, 29.5, 29.6, 31.9, 33.2, 39.0, 40.5, 45.5, 47.9, 78.8, 118.9, 150, 156.1, 167.3, 173.1. Mass spectrum (c.i.) m/z 552 (MH^+), 478, 452.

N-[2-(*tert*-Butyloxycarbonylamino)ethyl]-N-[5-(3,3-dimethylacrylamido)pentyl]dodecanamide (195)

This amide was prepared and purified by the above method (75%). ν_{max} 3350, 2950, 1710, 1630 cm^{-1}. ^{1}H n.m.r. δ_H 0.88, t, 3H; 1.25, s, 18H; 1.43, s, 11H; 1.6, m, 4H; 1.8, s, 3H; 2.15, s, 3H; 2.28, t, 2H; 3.1, m, 8H; 5.3, bs, 1H; 5.60, s, 1H; 6.2, bs, 1H. ^{13}C n.m.r. δ_C 13.8, 19.4, 22.3, 23.9, 24.7, 25.2, 26.8, 28.1, 29.0, 29.2, 29.3,

31.6, 32.8, 38.6, 39.0, 44.9, 45.2, 48.3, 78.6, 118.5, 149.9, 156.0, 167.0, 173.7. Mass spectrum (c.i.) m/z 510 (MH^+), 436, 410, 368.

N-[5-(*tert*-Butyloxycarbonylamino)pentyl]-N-[2-(3,3-dimethylacrylamido)ethyl]dodecanamide (196)

This amide was prepared by the above method (94%). ν_{max} 3350, 2950, 1630 cm^{-1}. ^1H n.m.r. δ_H 0.87, t, 3H; 1.28, s, 16H; 1.45, s, 9H; 1.65, m (broad), 8H, 1.80, s, 3H; 2.10, s, 3H; 2.30, t, 2H; 3.1, m (broad), 8H; 4.80, bt, 1H; 5.55, s, 1H; 6.6, bs, 1H. ^{13}C n.m.r. δ_C 13.8, 19.4, 22.4, 23.7, 25.3, 26.8, 28.1, 29.0, 29.2, 29.3, 30.0, 31.6, 32.9, 38.5, 40.0, 48.3, 78.6, 118.4, 150.0, 155.9, 167.2, 174.3. Mass spectrum (c.i.) m/z 510 (MH^+), 454, 436, 410.

N-[2-(*tert*-Butyloxycarbonylamino)ethyl]-N-[2-(3,3-dimethylacrylamido)ethyl]acetamide (197)

This amide was prepared by the above method (98%). ν_{max} 3350, 2990, 1710, 1670, 1630 cm^{-1}. ^1H n.m.r. δ_H 1.42, s, 9H; 1.82, s, 3H; 2.15, bs, 6H; 3.3, m (broad), 8H, 5.4, bs, 1H; 5.58, s, 1H; 6.75, bs, 1H. ^{13}C n.m.r. δ_C19.5, 21.2, 26.9, 28.2, 38.2, 45.3, 45.9, 49.0, 79.1, 118.3, 150.5, 156, 167.4, 171.9. Mass spectrum (c.i.) m/z 328 (MH^+), 285 ($MH^+-C_2H_3O$).

N-[2-(*tert*-Butyloxycarbonylamino)ethyl]-N-[2-(3,3-dimethylacrylamido)ethyl]dodecanamide (198)

This amide was prepared and purified by the described method (93%). ν_{max} 3340, 2950, 1710, 1670 cm^{-1}. ^1H n.m.r.

δ_H 0.85, t, 3H; 1.33, s, 14H; 1.42, s, 9H; 1.6, m, 4H; 1.85, s, 3H; 2.20, s, 3H; 2.35, t, 2H; 3.3, m, 8H, 5.4, bs, 1H; 5.60, s, 1H; 6.6, bs, 1H. ^{13}C n.m.r. δ_C13.9, 19.6, 22.5, 25.4, 27.0, 28.2, 29.2, 29.4, 31.7, 32.9, 38.4, 45.3, 48.2, 48.3, 79.1, 118.4, 150.7, 156.0, 167.5, 174.7. Mass spectrum (c.i.) m/z 468 (MH^+), 412, 394, 368.

N-Substituted Amides (233) and (234)

The N-substituted amides (233) and (234) were prepared from the requisite acyl chlorides and N-(*tert*-butyloxylcarbonyl)-1,5-diaminopentane hydrochloride (175) according to the standard procedure as described for the N,N-disubstituted amides.

N-[5-(*tert*-Butyloxycarbonylamino)pentyl]-3,3-dimethylacrylamide (233)

Yield (98%), b.p. 130-140° (0.003 mm). (Found: C, 61.6; H, 10.1; N, 9.8. $C_{15}H_{28}N_2O_3.\frac{1}{2}H_2O$ requires C, 61.4; H, 10.0; N, 9.6%). ν_{max} 3350, 2950, 1695, 1670, 1640 cm^{-1}. ^1H n.m.r. δ_H 1.4, s, 15H; 1.80, s, 3H; 2.15, s, 3H; 3.1, m, 4H; 4.65, bs, 1H; 5.56, s, 1H; 5.8, bs, 1H. ^{13}C n.m.r. δ_C19.5, 23.8, 26.9, 28.2, 29.1, 29.6, 38.7, 40.2, 78.8, 118.6, 150.0, 156.0, 167.1. Mass spectrum (c.i.) m/z 285 (MH^+).

N-[5-(*tert*-Butyloxycarbonylamino)pentyl]dodecanamide (234)

This amide was purified by recrystallization (83%) m.p. (50% benzene/pet ether) 66-66.5° b.p. 173-181° (0.003 mm).

(Found: C, 68.7; H, 11.5; N, 7.2. $C_{22}H_{44}N_2O_3$ requires C, 68.7; H, 11.3; N, 7.3%). ν_{max} 3330, 3310, 2950, 1690, 1645, 1540 cm^{-1}. ^1H n.m.r. δ_H 0.90, t, 3H; 1.25, s, 18H; 1.46, 15H; 2.18, t, 2H; 3.18, m, 4H; 4.62, bs, 1H; 5.80, bs, 1H. ^{13}C n.m.r. δ_C 14.0, 22.5, 23.8, 25.7, 28.3, 29.1, 29.2, 29.5, 29.6, 31.8, 36.7, 39.1, 40.2, 78.9, 156.1, 173.2. Mass spectrum (c.i.) m/z 385 (MH^+), 370, 329, 285.

Primary Amines

The primary amines were prepared from the requisite N,N-disubstituted amides (153 and 182-198) by the following standard procedure.

The amines (154 and 199-215) were used immediately and without further purification in the amidination. Initially of high purity (t.l.c.), the amines decomposed within 3 days even when stored under nitrogen at 4°. The major decomposition product had a higher t.l.c. R_f yet it was still a primary amine (positive to the ninhydrin test). ν_{max} 3350, 2950, 1725, 1660, 1630 cm^{-1}.

N-(6-Aminohexyl)-N-[3-(3,3-dimethylacrylamido)propyl]-dodecanamide (154)

Neat trifluoroacetic acid (3 ml) was added to 1.23 g (2.29 mmol) of the amide (153) and the solution was stirred for 30 min with occasional cooling. The solution was cooled over ice, then 5% aqueous sodium hydroxide was added until the solution was alkaline to pH paper. The alkaline solution was extracted with

dichloromethane (4 x 10 ml) then backwashed with 5% sodium hydroxide followed by drying and evaporation to afford 1.03 g (100%) of the amine (154) as an oil. ν_{max} 3350, 2950, 1670, 1630 cm^{-1}. ^{1}H n.m.r. δ_H 0.87, t, 3H; 1.27, bs, 28H; 1.82, s, 3H; 2.13, s, 3H; 2.30, t, 2H, 2.67, bt, 2H; 3.3, m, 6H; 5.62, s, 1H; 6.77, bs, 1H. ^{13}C n.m.r. δ_C 14.2, 19.7, 22.7, 25.7, 26.7, 26.8, 27.6, 29.2, 29.4, 29.6, 32.0, 33.2, 35.5, 42.4, 42.5, 45.8, 47.9, 119.3, 149.5, 167.1, 173.8.

N-(6-Aminohexyl)-N-[3-(3,3-dimethylacrylamido)propyl]octadecanamide (199)

This amine was prepared by the above procedure (91%). ν_{max} 3300, 2950, 1670, 1630 cm^{-1}. ^{1}H n.m.r. δ_H 0.87, t, 3H; 1.27, bs, 32H; 1.6, m, 8H; 1.81, s, 3H; 2.11, s, 3H; 2.25, t, 2H; 2.67, bt, 2H; 3.3, m, 6H; 5.61, s, 1H; 6.78, bs, 1H. ^{13}C n.m.r. δ_C 13.9, 19.4, 22.5, 25.5, 26.4, 26.6, 26.8, 27.2, 28.8, 29.1, 29.3, 29.4, 31.7, 32.9, 35.1, 41.7, 42.1, 47.6, 118.9, 149.5, 167.0, 173.7.

N-(6-Aminohexyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadec-9-enamide (200)

This amine was prepared by the above procedure (88%). ν_{max} 3300, 2950, 1670, 1630 cm^{-1}. ^{1}H n.m.r. δ_H 0.89, t, 3H; 1.26, s, 24H; 1.63, m (broad), 10H; 1.83, s, 3H; 2.0, m, 6H; 2.15, s, 3H; 2.25, t, 2H; 2.75, bt, 2H; 2.95, s, 2H (exchanged by D_2O); 3.25, m, 6H; 5.28, t, 2H; 5.62, s, 1H; 6.85, bt, 1H (exchanged by D_2O).

N-(5-Aminopentyl)-N-[3-(3,3-dimethylacrylamido)propyl]-acetamide (201)

This amine was prepared by the above procedure but worked up with 10% 2-propanol/chloroform (88%). ν_{max} 3350, 1670, 1640 cm^{-1}. ^{1}H n.m.r. δ_H 1.5, m(broad), 8H; 1.70, bs, 2H (exchanged by D_2O); 1.80, s, 3H; 2.08, s, 3H; 2.10, s, 3H; 2.65, bt, 2H; 3.3, m, 6H; 6.05, s, 1H; 7.15, bs, 1H (exchanged by D_2O). ^{13}C n.m.r. δ_C 19.7, 21.4, 24.3, 27.1, 27.5, 28.8, 35.4, 42.0, 42.3, 48.3, 119.2, 149.9, 167.3, 171.2.

N-(5-Aminopentyl)-N-[3-(3,3-dimethylacrylamido)propyl]-dodecanamide (202)

This amine was prepared by the usual procedure (94%). ν_{max} 3350, 2950, 1670, 1630 cm^{-1}. ^{1}H n.m.r. δ_H 0.89, t, 3H; 1.25, s, 22H; 1.55, m. 8H; 1.80, s, 3H; 2.13, s, 3H; 2.28, t, 2H; 2.75, bs, 4H (2H exchanged by D_2O); 3.3, m, 6H; 5.60, s, 1H; 6.82, bt, 1H (exchanged by D_2O). ^{13}C n.m.r. δ_C 13.9, 19.5, 22.5, 24.0, 25.5, 26.8, 27.2, 28.7, 29.1, 29.3, 29.4, 31.7, 33.0, 35.2, 41.5, 42.1, 45.4, 47.6, 118.9, 149.6, 167.0, 173.7.

N-(5-Aminopentyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadecanamide (203)

This amine was prepared by the above procedure (88%). ν_{max} 3300, 2930, 1630 cm^{-1}. ^{1}H n.m.r. δ_H0.88, t, 3H; 1.25, s, 30H; 1.5, m (broad), 8H; 1.80, s, 3H; 2.13, s, 3H; 2.28, t, 2H; 2.45, s, 2H; 2.65, m, 2H; 3.1, m, 6H; 5.60, s, 1H; 6.82, bs, 1H. ^{13}C n.m.r. δ_C13.9, 19.5, 22.5, 24.0, 25.5, 27.3, 29.2, 29.3, 29.5, 31.7, 33.0, 35.2, 41.6, 42.1, 47.6, 118.9, 149.6, 167.0, 173.7.

N-(5-Aminopentyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadec-9-enamide (204)

This amine was prepared by the above procedure (86%). ν_{max} 3330, 2930, 1635 cm^{-1}. ^{1}H n.m.r. δ_H0.88, t, 3H; 1.25, s, 24H; 1.6, m (broad), 8H; 1.80, s, 3H; 1.95, m, 4H; 2.13, s, 3H; 2.28, t, 2H; 2.75, bs, 2H; 3.1, m, 6H; 5.30, t, 2H; 5.60, s, 1H; 6.82, bs, 1H. ^{13}C n.m.r. δ_C13.9, 19.5, 22.5, 24.0, 25.5, 26.8, 27.0, 27.3, 28.8, 29.0, 29.1, 29.3, 29.5, 31.7, 33.0, 35.1, 41.6, 42.1, 47.6, 118.9, 129.5, 129.8, 149.6, 167.0, 173.7.

N-(4-Aminobutyl)-N-[3-(3,3-dimethylacrylamido)propyl]-dodecanamide (205)

This amide was prepared by the above procedure (98%). ν_{max} 3350, 2850, 1670, 1630 cm^{-1}. ^{1}H n.m.r. δ_H 0.87, t, 3H; 1.3, s, 16H; 1.6, m, 8H (2H exchanged by D_2O); 1.81, s, 3H;

2.15, s, 3H; 2.3, t, 2H; 2.6, t, 2H; 3.2, m, 8H; 5.60, s, 1H; 7.2, bs, 1H (exchanged by D_2O). ^{13}C n.m.r. δ_C13.9, 19.5, 22.4, 25.5, 26.3, 26.8, 27.3, 29.1, 29.4, 31.7, 33.0, 35.1, 41.6, 42.0, 47.5, 119.0, 149.5, 167.0, 173.8.

N-(4-Aminobutyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadecanamide (206)

This amine was prepared by the above procedure (94%). ν_{max} 3350, 2950, 1670, 1630 cm^{-1}. ^1H n.m.r. δ_H 0.90, t, 3H; 1.20, s, 30H; 1.58, m (broad), 6H; 1.80, s, 3H; 2.15, s, 3H; 2.30, t, 2H; 2.7, t, 2H; 3.6, m (broad), 6H; 5.6, s, 1H; 6.70, bs, 1H. ^{13}C n.m.r. δ_C 14.0, 19.5, 22.6, 25.6, 26.4, 26.9, 27.3, 29.2, 29.4, 29.5, 31.8, 33.1, 35.1, 41.7, 42.0, 47.6, 119.0, 167.0, 173.9.

N-(4-Aminobutyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadec-9-enamide (207)

This amine was prepared by the above procedure (98%). ν_{max} 3350, 2850, 1670, 1630 cm^{-1}. ^1H n.m.r. δ_H0.88, t, 3H; 1.26, s, 22H; 1.6, m (broad), 6H; 1.80, s, 3H; 2.00, m, 4H; 2.13, s, 3H; 2.30, t, 2H; 2.70, bt, 2H; 3.3, m (broad), 6H; 5.34, t, 2H; 5.60, s, 1H; 6.65, bt, 1H. ^{13}C n.m.r. δ_C14.0, 17.2, 19.5, 22.5, 25.5, 26.4, 26.9, 27.3, 29.0, 29.2, 29.4, 29.5 30.7, 31.7, 32.4, 33.0, 35.1, 37.4, 41.6, 42.0, 47.5, 119.0, 129.1, 129.8, 167.0, 173.9.

N-(2-Aminoethyl)-N-[3-(3,3-dimethylacrylamido)propyl]-dodecanamide (208)

This amide was prepared by the above procedure (98%). ν_{max} 3340, 2950, 1670, 1630 cm^{-1}. ^1H n.m.r. δ_H0.90, t, 3H;

1.28, s, 16H; 1.75, s, 4H; 1.80, s, 3H; 2.14, s, 3H; 2.35, t, 2H; 2.85, t, 2H; 3.4, m, 6H; 5.60, s, 1H; 6.61, bt, 1H.

N-(2-Aminoethyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadecanamide (209)

This amine was prepared by the above procedure (98%). ν_{max} 3350, 2950, 1640 cm^{-1}. ^{1}H n.m.r. δ_H 0.85, t, 3H; 1.25, s, 28H; 1.65, m, 4H; 1.80, s, 3H; 2.15, s, 3H; 2.4, t, 2H; 2.95, t, 2H; 3.4, m, 6H; 5.6, s, 1H; 6.7, bt, 1H.

N-(2-Aminoethyl)-N-[3-(3,3-dimethylacryamido)propyl]-octadec-9-enamide (210)

This amine was prepared by the above procedure (98%). ν_{max} 3350, 2950, 1670, 1630 cm^{-1}. ^{1}H n.m.r. δ_H0.85, t, 3H; 1.30, s, 24H; 1.70, m, 6H, (2H exchanged by D_2O); 1.85, s, 3H; 2.0, m, 4H; 2.1, s, 3H; 2.35, t, 2H; 2.88, t, 2H; 3.45, m, 6H; 5.4, t, 2H; 5.6, s, 1H; 6.7, bs, 1H (exchanged by D_2O).

N-(5-Aminopentyl)-N-[5-(3,3-dimethylacrylamido)pentyl]-dodecanamide (211)

This amine was prepared by the above procedure (91%). ν_{max} 3330, 2950, 1670, 1635 cm^{-1}. ^{1}H n.m.r. δ_H0.83, t, 3H; 1.25, s, 24H; 1.37, m (broad), 6H; 1.76, s, 3H; 2.15, s, 3H; 2.25, t, 2H; 2.73, bt, 2H; 3.3, m, 6H; 5.58, s, 1H; 6.1, bs, 3H. ^{13}C n.m.r. δ_C14.1, 19.7, 22.7, 24.3, 25.6, 27.1, 27.3, 28.9, 29.1, 29.3, 29.5, 29.6, 31.9, 33.2, 39.0, 41.9, 45.2, 47.9, 118.9, 150, 167.4, 173.1.

N-(2-Aminoethyl)-N-[5-(3,3-dimethylacrylamido)pentyl]-dodecanamide (212)

This amine was prepared by the above procedure (97%). ν_{max} 3330, 2950, 1670, 1630 cm^{-1}. ^{1}H n.m.r. δ_H0.82, t, 3H; 1.26, s, 18H; 1.6, m, 6H; 1.76, s, 3H; 2.15, s, 3H; 2.25, t, 2H; 2.73, bt, 2H; 3.3, m, 6H; 5.58, s, 1H; 6.0, bs, 3H. ^{13}C n.m.r. δ_C14.1, 19.7, 22.7, 25.6, 27.1, 28.9, 29.4, 29.6, 29.7, 31.9, 33.2, 33.4, 39.0, 40.7, 45.5, 48.6, 118.6, 167.3, 174.8.

N-(5-Aminopentyl)-N-[2-(3,3-dimethylacrylamido)ethyl]-dodecanamide (213)

This amine was prepared by the above procedure (98%). ν_{max} 3350, 2950, 1640 cm^{-1}. ^{1}H n.m.r. δ_H0.85, t, 3H; 1.24, s, 16H; 1.35, bs, 8H; 1.73, s, 2H (exchanged by D_2O); 1.80, s, 3H; 2.12, s, 3H; 2.20, t, 2H; 2.68, t, 2H; 3.3, m, 6H; 5.50, s, 1H; 6.55, bs, 1H (exchanged by D_2O).

N-(2-Aminoethyl)-N-[2-(3,3-dimethylacrylamido)ethyl]-acetamide (214)

This amine was prepared by the above procedure but worked up with brine and 5% 2-propanol/chloroform after the normal extraction with dichloromethane.

The dichloromethane extract afforded a high R_f compound (19%). ν_{max} 3450, 3350, 2950, 1735, 1640 cm^{-1}.

The 2-propanol/chloroform extract afforded the requried amine (13%). ν_{max} 3350, 2950, 1670, 1640 cm^{-1}.

N-(2-Aminoethyl)-N-[2-(3,3-dimethylacrylamido)ethyl]-dodecanamide (215)

This amine was prepared by the above procedure with the usual work up (86%). ν_{max} 3350, 2950, 1640 cm^{-1}. ^1H n.m.r. δ_H0.82, t, 3H; 1.20, s, 15H; 1.78, bs, 7H (2H exchanged by D_2O); 2.10, s, 3H; 2.30, m, 2H; 2.80, t, 2H; 3.45, m (broad), 6H; 5.50, s, 1H; 6.5, bs, 1H (exchanged by D_2O). ^{13}C n.m.r. δ_C14.1, 19.8, 22.7, 25.5, 27.1, 29.4, 29.5, 29.6, 31.9, 33.3, 38.8, 40.7, 45.4, 51.2, 118.6, 150.6, 167.6, 175.2.

N-(5-Aminopentyl)-3,3-dimethylacrylamide (235)

This amine was prepared by the above procedure (81%). ν_{max} 3300, 2950, 1670, 1630 cm^{-1}. ^1H n.m.r. δ_H1.42, s, 8H; 1.82, s, 3H; 2.05, s, 3H; 2.65, t, 2H; 3.25, m, 2H; 5.6, s, 1H; 6.45, bs, 1H. ^{13}C n.m.r. δ_C19.2, 23.8, 26.6, 29.1, 32.9, 38.5, 41.5, 118.5, 149.1, 166.8.

N-(5-Aminopentyl)dodecanamide (236)

This amine was prepared by the above procedure (56%). m.p. 80-81°. ν_{max} 3350, 2950, 1640 cm^{-1}. ^1H n.m.r. δ_H1.89, t, 3H; 1.24, s, 16H; 1.40, bs, 10H; 2.2, m, 2H; 2.7, bs, 2H; 3.25, m, 2H; 6.0, bs, 1H. ^{13}C n.m.r. δ_C 13.9, 22.5, 24.0, 25.7, 29.2, 29.3, 29.4, 31.7, 36.6, 39.1, 41.8, 173.1.

Acarnidines

The acarnidines (155 and 216-232) were prepared from the requisite primary amines (154 and 199-215) by the following standard procedure.

N-(6-Guanidinohexyl)-N-[3-(3,3-dimethylacrylamido)propyl]-dodecanamide (155)

A solution of 1.03 g (2.36 mmol) of the primary amine (154) and 0.65 g (3.00 mmol) of S-methylisothiouronium iodide (119) in 15 ml of ethanol were stirred for 34 h at room temperature. The ethanol was removed by evaporation at 30° and the residue was taken up in 30% saturated aqueous sodium iodide solution (to prevent emulsification) and extracted with chloroform (4 x 10 ml). The combined chloroform extracts were backwashed with saturated aqueous sodium iodide before drying and evaporation to an oil (1.34 g, 93%). This was the only acarnidine that was converted to the chloride by ion exchange chromatography (*vide infra*) before purification by gel permeation chromatography on Fractogel PGM 2000 (Merck, 140-230 mesh). The crude acarnidine (155) (104 mg), dissolved in 0.8 ml of ethanol was washed onto the 10.5 x 1.0 cm Fractogel column and eluted with ethanol at a flow rate of 0.2 ml min^{-1} to afford 69 mg (67%) of pure acarnidine (155). [Found: (h.r.f.a.b.) MH^+, 480.4266. $C_{27}H_{54}N_5O_2$ requires 480.4277]. ν_{max} 3300, 1660, 1630 cm^{-1}. λ_{max} (ethanol) 209 nm (ε 22 000), λ_{max} (KOH, ethanol) 213 nm (ε 27 000). ^1H n.m.r. δ_H0.87, t, 3H; 1.27, s, 22H; 1.6, m, 6H; 1.82, s, 3H; 2.13, s, 3H; 2.30, t, 2H; 3.27, m (broad), 8H; 5.62, s, 1H; 7.15, bs, 1H (exchanged by D_2O); 7.0-8.5, broad), 6H (exchanged by D_2O). ^{13}C n.m.r. δ_C13.9, 19.8, 22.5, 25.6, 26.1, 26.2, 26.9, 29.2, 29.4, 31.9, 33.3, 36.3, 41.7, 42.5, 45.9, 48.2, 118.5, 151.3, 157.7, 168.0, 174.2. The carbon atoms α-to the nitrogen atoms

were very broad. Data was collected at 0° and 56° without substantially improving the peak shapes. Mass spectrum (f.a.b.) m/z 480 (100%, MH^+); 479 (6, MH^+-2H); 452 (6, MH^+-28); 367 (6, MH^+-$Me_2C{=}CHCONHCH_2$); 296 (5, MH^+-$C_{12}H_{23}O$); 281 (6); 182 (7); 142 (26, $C_7H_{16}N_3$); 140 (26, $C_8H_{14}NO$); 128 (20, $C_6H_{14}N_3$); 114 (10, $C_5H_{12}N_3$); 100 (20, $C_4H_{10}N_3$); 86 (18, $C_3H_8N_3$); 83 (30, C_5H_7O).

Other techniques were explored in attempts to purify the acarnidine.

(i) Preparative t.l.c. on silica gel. The crude acarnidine (155) (60 mg) was chromatographed on a 20 x 10 cm plate using 10% methanol/chloroform (twice). A small amount of acarnidine (155) was isolated (10 mg) but impurities were still present. (^{13}C n.m.r.).

(ii) Column chromatography of silica gel. Elution with mixtures of chloroform, methanol and ammonium hydroxide (45:8:1 → 30:18:5) did not separate the acarnidine (155) from ninhydrin positive material. Furthermore, the recovery of material from the column was poor.

(iii) Column chromatography on Florisil. Elution with mixtures of chloroform, methanol and ammonium hydroxide did not separate the acarnidine (155) from ninhydrin positive material.

(iv) Ion exchange chromatography on Zeo-Karb 225 (H^+) (> 200 mesh). Elution with aqueous formic and hydrochloric acids (0.2-6M) did not afford the

acarnidine (155). The addition of a 10% proportion of ethanol in the eluent afforded the acarnidine (155) but in admixture with ninhydrin positive material.

(v) Ion exchange chromatography on Dowex 50W X8 (H^+) (50-100 mesh). Elution with mixtures of aqueous hydrochloric acid and ethanol afforded the acarnidine (155) in admixture with ninhydrin positive material (6M hydrochloric acid as a 10% solution in ethanol).

(vi) Ion exchange chromatography on Amberlyst 15 (H^+) (16-50 mesh). As for (v) above, but the mixture eluted with 5% 10M aqueous hydrochloric acid in ethanol.

(vii) Partitioning. Partition of the acarnidine (155) and amine impurity was attempted between ethyl acetate and Phosphate II buffer (pH 7.4)[102]. Only high R_f impurities were extracted into the organic phase. The phosphate buffer was washed with various proportions of ethyl acetate and dichloromethane in admixture. A high proportion of the ethyl acetate had no effect, whereas higher proportions of dichloromethane provided uniform extraction of the acarnidine (155) and amine impurities.

(viii) Reverse phase column chromatography (Waters-ODS; 37-70μ). Stepwise elution of water/methanol mixtures did not separate the acarnidine (155) from the amine impurity (10% water/methanol).

(ix) High performance liquid chromatography. A normal phase cyanopropylsilane column (2-propanol/chloroform) and a reverse phase octadecylsilane column (aqueous-methanol or tetrahydrofuran/methanol or chloroform/methanol) were not able to purify the acarnidine (155). Chromatography on the octylsilane column improved the peak shapes and decreased the long retention times observed on the octadecylsilane column. Some separation of the acarnidine (155) (Sakaguchi test positive) and ninhydrin positive compounds occurred.

(x) Column chromatography on Sephadex LH-20. Elution with ethanol did not separate the acarnidine (155) from the amine. Aqueous ethanol increased the speed of elution with no purification.

N-(6-Guanidinohexyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadecanamide (216)

This acarnidine was prepared by the above procedure and purified as the hydriodide on Fractogel (60%). [Found: (h.r.f.a.b) MH^+, 564.5231. $C_{33}H_{66}N_5O_2$ requires 564.5216]. ν_{max} 3300, 3200, 2900, 1660, 1630 cm^{-1}. λ_{max} (ethanol) 210 nm (ε 24 000). ^1H n.m.r. δ_H 0.87, t, 3H; 1.27, bs, 32H; 1.6, m, 8H; 1.81, s, 3H; 2.11, s, 3H; 2.25, t, 2H; 3.3, m (broad), 8H; 5.61, s, 1H; 7.2, bs, 4H; 7.75, bs, 2H. ^{13}C n.m.r. δ_C14.0, 19.7, 22.6, 25.6, 26.0, 26.2, 27.0, 28.4, 28.7, 28.8, 29.0, 29.2, 29.6, 31.8, 33.1, 118.8, 150.1, 157.6, 167.6, 173.8.

N-(6-Guanidinohexyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadec-9-enamide (217)

This acarnidine was prepared by the above procedure (35%). [Found: (h.r.f.a.b.) MH^+, 562.5052. $C_{33}H_{64}N_5O_2$ requires 562.5060]. ν_{max} 3300, 3200, 2950, 1660, 1630 cm^{-1}. λ_{max} (ethanol) 210 nm (ε 24 000), λ_{max} (KOH, ethanol) 215 (ε 19 000). ^1H n.m.r. δ_H 0.89, t, 3H; 1.27, s, 24H; 1.6, m (broad), 10H; 1.83, s, 3H; 2.0, m. 6H; 2.16, s, 3H; 2.26, t, 2H; 3.25, m (broad), 8H; 5.29, t, 2H; 5.68, s, 1H; 6.7-8.5, m, 6H. ^{13}C n.m.r. δ_C13.9, 19.7, 22.5, 25.6, 25.9, 26.0, 26.1, 27.0, 28.6, 28.7, 29.0, 29.1, 29.3, 29.5, 31.7, 32.4, 33.1, 118.8, 129.5, 129.8, 150.1, 167.5, 173.8.

N-(5-Guanidinopentyl)-N-[3,3-dimethylacrylamido)propyl]-acetamide (218)

This acarnidine was prepared by the above procedure but worked up with 10% 2-propanol/chloroform. After chromatography on Fractogel (2-propanol) the appropriate fractions were recombined and chromatographed twice by preparative t.l.c. (25% methanol in chloroform) before obtaining the pure acarnidine (10%). ν_{max} 3300, 3200, 2950, 1660, 1530 cm^{-1}. λ_{max} 218 nm (ε 27 000), λ_{infl} 208 nm. ^1H n.m.r. $\delta_H(CD_3OD)$ 1.58, m, 8H; 1.80, s, 3H; 1.09, s, 3H; 1.20, s, 3H, 3.3, m, 8H (under methanol-d_4) 5.66, s, 1H. ^{13}C n.m.r. δ_C20.0, 21.5, 24.9, 25.3, 27.1, 28.1, 28.7, 29.4, 29.6, 29.8, 37.5, 37.7, 42.4, 46.7, 119.5, 151.9, 158.6, 169.8, 173.3. Mass spectrum (f.a.b.) m/z 462 (15%), 326 (MH^+, 100).

N-(5-Guanidinopentyl)-N-[3-(3,3-dimethylacrylamido)propyl]-dodecanamide (219)

This acarnidine was prepared by the usual procedure and purified on Fractogel (ethanol) (40%). [Found: (h.r.f.a.b) MH^+, 466.4111. $C_{26}H_{52}N_5O_2$ requires 466.4121]. ν_{max} 3300, 3200, 2950, 1660, 1630 cm^{-1}. λ_{max} (ethanol) 217 nm (ε 26 000), $\lambda_{infl.}$ 208 nm. ^1H n.m.r. δ_H 0.88, t, 3H; 1.25, s, 18H; 1.6, m, 8H; 1.80, s, 3H; 2.13, s, 3H; 2.28, t, 2H; 3.3, m (broad), 8H; 5.60, s, 1H; 5.2-7.6, broad, 6H. ^{13}C n.m.r. δ_C 13.7, 19.6, 22.3, 25.3, 26.8, 29.0, 29.3, 31.5, 32.9, 35.8, 36.3, 118, 150.1, 157.1, 167.5, 173.6. Mass spectrum (f.a.b.) m/z 466 (100%, MH^+); 458 (10); 438 (5); 350 (4, $M-C_5H_{13}N_3$); 267 (5); 140 (15); 128 (10); 126 (8); 114 (11); 100 (7); 86 (19); 83 (40).

N-(5-Guanidinopentyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadecanamide (220)

This acarnidine was prepared by the above procedure and purified on Fractogel (2-propanol) (40%). [Found: (h.r.f.a.b.) MH^+, 550.5079. $C_{32}H_{64}N_5O_2$ requires 550.5060]. ν_{max} 3300, 3200, 2950, 1660, 1630 cm^{-1}. λ_{max} (methanol) 208 (ε 20 000), λ_{max} (KOH, methanol) 216 nm (ε 16 000). ^1H n.m.r. δ_H 0.88, t, 3H, 1.25, s, 30H; 1.6, m, 8H; 1.80, s, 3H; 2.13, s, 3H; 2.28, t, 2H; 3.2, m (broad), 8H; 5.60, s, 1H; 5.6-7.8, broad, 6H. ^{13}C n.m.r. δ_C 13.8, 19.6, 22.4, 25.4, 26.9, 29.0, 29.4, 31.6, 32.9, 33.0, 36.2, 36.4, 118.7, 150.0, 157.2, 167.5, 173.6.

N-(5-Guanidinopentyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadec-9-enamide (221)

This acarnidine was prepared and purified by the above procedure (60%). [Found: (h.r.f.a.b.) MH^+, 548.4883. $C_{32}H_{62}N_5O_2$ requires 548.4900]. ν_{max} 3300, 3200, 2950, 1660, 1630 cm^{-1}. ^1H n.m.r. δ_H0.88, t, 3H; 1.27, s, 22H; 1.6, m (broad), 10H; 1.83, s, 3H; 2.0, m, 6H; 2.15, s, 3H; 2.27, t, 2H; 3.3, m. (broad), 8H; 5.30, t, 2H; 5.68, s, 1H; 6.8-8.6, m, 6H. ^{13}C n.m.r. δ_C 13.9, 19.6, 22.4, 25.4, 27.0, 29.0, 29.3, 29.5, 31.6, 33.0, 41.3, 129.4, 129.7, 150.1, 157.4, 167.5, 173.7.

N-(4-Guanidinobutyl)-N-[3-(3,3-dimethylacrylamido)propyl]-dodecanamide (222)

This acarnidine was prepared by the above procedure (45%). [Found: (h.r.f.a.b.) MH^+, 452.3981. $C_{25}H_{50}N_5O_2$ requires 452.3964]. ν_{max} 3300, 3100, 2950, 1670, 1630 cm^{-1}. λ_{max} (methanol) 209 nm (ε 25 000). ^1H n.m.r. δ_H0.85, t, 3H; 1.30, bs, 16H; 1.61, m (broad), 8H; 1.80, s, 3H; 2.15, s, 3H; 2.30, bt, 2H; 3.30, bs, 8H; 5.70, s, 1H; 6.7-9.2, bd, 6H (exchanged by D_2O). ^{13}C n.m.r. δ_C14.1, 19.9, 22.7, 25.7, 26.0, 26.1, 26.3, 27.2, 27.3, 29.4, 29.7, 31.9, 33.3, 118.7, 151.0, 157.8, 167.8, 174.0.

N-(4-Guanidinobutyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadecanamide (223)

This acarnidine was prepared by the above procedure (30%). [Found: (h.r.f.a.b.) MH^+, 536.4914. $C_{31}H_{62}N_5O_2$

requires 536.4903]. ν_{max} 3300, 3200, 2950, 1670, 1630 cm^{-1}. λ_{max} (methanol) 209 nm (ε 22 000). ^{1}H n.m.r. δ_H0.86, t, 3H; 1.24, bs, 28H; 1.24, bs, 28H; 1.6, m (broad), 8H; 1.80, s, 3H; 2.15, s, 3H; 2.25, bs, 2H; 3.3, bs, 8H; 5.65, s, 1H; 6.5-8.5, (broad), 6H. ^{13}C n.m.r. δ_C14.1, 19.9, 22.7, 25.5, 25.7, 26.1, 26.2, 27.2, 29.4, 29.7, 32.0, 33.0, 41.3, 118.9, 151.0, 157.7, 167.8, 173.9.

N-(4-Guanidinobutyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadec-9-enamide (224)

This acarnidine was prepared by the above procedure (50%). [Found: (h.r.f.a.b.) MH^+, 534.4698. $C_{31}H_{60}N_5O_2$ requires 534.4747]. ν_{max} 3300, 3200, 2950, 1670, 1630 cm^{-1}. λ_{max} (methanol) 207 nm (ε 21 000). ^{1}H n.m.r. δ_H0.80, t, 3H; 1.20, s,21H; 1.6, m, 6H; 1.80, s, 3H; 2.0, m (broad), 6H; 2.15, s, 3H; 2.40, bt, 2H; 3.0, m (broad), 8H; 5.3, t, 2H; 5.7, bs, 1H; 6.7-8.5, broad, 5H. ^{13}C n.m.r. δ_C14.1, 19.9, 22.7, 25.7, 25.8, 26.1, 26.4, 27.3, 29.4, 29.6, 29.8, 31.9, 33.3, 36.6, 36.9, 37.6, 119.0, 129.8, 130.0, 150.9, 157.8, 167.8, 174.0.

N-(2-Guanidinoethyl)-N-[3-(3,3-dimethylacrylamido)propyl]-dodecanamide (225)

This acarnidine was prepared by the above procedure (10%). [Found: (h.r.f.a.b.) MH^+, 424.3659. $C_{23}H_{46}N_5O_2$ requires 424.3651]. ν_{max} 3350, 2950, 1670, 1630 cm^{-1}. λ_{max} (methanol) 207 nm (ε 8000). ^{1}H n.m.r. δ_H0.83, t, 3H; 1.20, s, 14H; 1.6, m, 4H; 1.82, s, 3H; 2.09, s, 3H;

2.29, bt, 2H; 3.4, m (broad), 8H; 5.62, s, 1H; 6.0-8.0 (broad), 6H. ^{13}C n.m.r. δ_C14.1, 20.1, 22.7, 25.4, 27.3, 29.4, 29.6, 31.3, 33.3, 36.6, 39.5, 46.4, 47.7, 118.5, 151.5, 157.8, 168.0, 175.3.

N-(2-Guanidinoethyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadecanamide (226)

This acarnidine was prepared by the above procedure (15%) and eluted last on Fractogel chromatography. [Found: (h.r.f.a.b.) MH^+, 508.4615. $C_{29}H_{58}N_5O_2$ requires 508.4590]. ν_{max} (methanol) 219 nm (ε 33 000), $\lambda_{infl.}$ 208 nm. ^1H n.m.r. δ_H0.85, t, 3H; 1.25, s, 26H; 1.6, m, 6H; 1.80, s, 3H; 2.08, s, 3H, 2.25, bt, 2H; 3.4, m (broad), 8H; 5.68, s, 1H; 6.5-7.7, (broad), 6H. ^{13}C n.m.r. δ_C14.1, 20.1, 22.7, 25.4, 27.3, 29.4, 29.8, 32.0, 33.3, 33.4, 118.5, 151.7, 157.9, 168.0, 175.3.

N-(2-Guanidinoethyl)-N-[3-(3,3-dimethylacrylamido)propyl]-octadec-9-enamide (227)

This acarnidine was prepared by the above method, but two Sakaguchi test positive compounds were isolated. The guanidino compound that eluted first from the Fractogel [t.l.c. R_f (25% methanol/chloroform) = 0.50] was also positive to ninhydrin (orange colour compared to the more usual plum colour of the primary amines) (15%). ^1H n.m.r. δ_H0.81, t, 3H; 1.23, s, 17H; 1.6, m, 6H; 1.81, s, 3H; 2.0, m, 6H; 2.15, s, 3H; 2.40, bt, 2H; 3.0, m (broad), 8H; 5.3, t, <2H; 5.68, s, 1H; 6.2-8.8, broad, 6H. ^{13}C n.m.r. δ_C14.0, 19.7, 22.6, 25.2, 25.5, 27.1, 28.9, 29.2, 29.4, 29.6, 31.8,

33.0, 35.9, 36.4, 39.2, 45.6, 48.3, 118.1, 118.4, 129.7, 129.9, 151.0, 151.6, 158.1, 167.7, 168.3, 174.8.

The guanidino compound that eluted second from the Fractogel [t.l.c. R_f (25% methanol/chloroform) = 0.58] was consistent with the acarnidines previously isolated except for the smaller 1ω9 olefin ^1H n.m.r. integral (10%). ν_{max} 3300, 2950, 1670, 1630 cm^{-1}. λ_{max} (methanol) 218 nm (ε 28 000), $\lambda_{infl.}$ 208 nm. ^1H n.m.r. δ_H 0.88, t, 3H; 1.24, s, 17H; 1.6, m, 4H; 1.82, s, 3H; 2.0, m, 4H; 2.15, s, 3H; 2.30, bs, 2H; 2.7, bs, 4H; 3.0, m (broad), 8H; 5.3, t, <2H; 5.67, s, 1H; 6.4-8.8, 6H. ^{13}C n.m.r. δ_C 14.1, 20.1, 22.7, 25.4, 27.3, 29.4, 29.5, 29.7, 31.9, 33.2, 33.3, 36.0, 36.4, 39.5, 47.5, 47.6, 118.5, 129, 130, 151.5, 157.7, 168.0, 175.3. Mass spectrum (f.a.b.) m/z 524 (4%); 506 (M^+,5%); 482 (15); 424 (100).

N-(5-Guanidinopentyl)-N-[5-(3,3-dimethylacrylamido)pentyl]-dodecanamide (228)

This acarnidine was prepared by the above method, but purified by Fractogel chromatography followed by preparative t.l.c. (20% methanol/chloroform)(15%). [Found: (h.r.f.a.b.) MH^+, 494.4441. $C_{28}H_{56}N_5O_2$ requires 494.4434]. ν_{max} 3350, 2950, 1670, 1630 cm^{-1}. λ_{max} (methanol) 216 nm (ε 32 000), $\lambda_{infl.}$ 208 nm. ^1H n.m.r. δ_H 0.87, t, 3H; 1.25, bs, 22H; 1.6, m, 8H; 1.80, s, 3H; 2.13, s, 3H; 2.30, bt, 2H; 3.3, m (broad), 8H; 5.60, s, 1H; 6.6-8.0, broad, 6H. ^{13}C n.m.r. δ_C 14.1, 20.1, 22.7, 24.4, 25.7, 27.3, 29.0, 29.4, 29.7, 32.0, 33.3, 33.4, 39.3, 118.8, 150.8, 157.5,

168.1, 173.8. Mass spectrum (f.a.b.) m/z 506 (5%); 494 (MH^+, 100).

N-(2-Guanidinoethyl)-N-[5-(3,3-dimethylacrylamido)pentyl]-dodecanamide (229)

This acarnidine was prepared by the usual method (10%). [Found: (h.r.f.a.b.) MH^+, 452.3959. $C_{25}H_{50}N_5O_2$ requires 452.3964]. ν_{max} 3300, 2950, 1670, 1630 cm^{-1}. λ_{max} (methanol) 218 nm (ε 27 000), $\lambda_{infl.}$ 207 nm. ^1H n.m.r. δ_H 0.88, t, 3H; 1.24, s, 14H; 1.6, m (broad), 10H; 1.84, s, 3H; 2.09, s, 3H; 2.26, t, 2H; 3.3, m (broad), 8H; 5.60, s, 1H; 6.18, bt, 1H; 6.4-8.5, broad, 5H. ^{13}C n.m.r. δ_C 14.1, 20.1, 22.7, 24.0, 25.4, 27.2, 29.2, 29.4, 29.5, 29.7, 31.9, 33.2, 38.9, 39.4, 46.5, 46.7, 49.9, 118.8, 150.9, 158.0, 167.9, 175.1.

N-(5-Guanidinopentyl)-N-[2-(3,3-dimethylacrylamido)ethyl]-dodecanamide (230)

This acarnidine was prepared by the above method but purified on Fractogel and preparative t.l.c. (20% methanol/chloroform) (10%). [Found: (h.r.f.a.b.) MH^+, 452.3979. $C_{25}H_{50}N_5O_2$ requires 452.3964]. ν_{max} 3350, 3200, 2950, 1670, 1630 cm^{-1}. λ_{max} (methanol) 220 nm (ε 27 000). ^1H n.m.r. δ_H 0.88, t, 3H; 1.20, s, 16H; 1.55, m, 10H; 1.80, s, 3H; 2.03, s, 3H; 2.26, m, 2H; 3.4, m (broad), 8H; 5.62, s, 1H; 6.5-8.0, broad, 6H. ^{13}C n.m.r. δ_C 14.1, 20.1, 22.7, 25.8, 27.3, 29.4, 29.5, 31.9, 33.4, 118.3, 152.0, 157.4, 168.3, 175.1.

N-(2-Guandinoethyl)-N-[2-(3,3-dimethylacrylamido)ethyl]-acetamide (231)

This acarnidine was prepared by the above method (extracted with 10% 2-propanol/chloroform) and purified only by preparative t.l.c. (25% methanol/chloroform). The major product was isolated pure (t.l.c.) but within 8 h it was observed to be decomposing (t.l.c.). Storage under nitrogen at 4° did not stabilize this acarnidine (5%). ν_{max} 3350, 2950, 1720 (increased with time but the peak was absent when the compound was just isolated) 1670, 1630 cm^{-1}. λ_{max} (methanol) 220 nm (ε 30 000), $\lambda_{infl.}$ 207 nm. ^{1}H n.m.r. δ_H (CD_3OD) 1.84, s, 3H; 2.08, s, 3H; 2.15, s, 3H; 3.6, m, 8H; 5.65, s, 1H. Mass spectrum (f.a.b.) m/z 451 (10%) 410 (15); 270 (MH^+, 100).

N-(2-Guanidinoethyl)-N-[2-(3,3-dimethylacrylamido)ethyl]-dodecanamide (232)

This acarnidine was prepared by the usual method and purified by Fractogel chromatography and preparative t.l.c. (20% methanol/chloroform) (20%). [Found: (h.r.f.a.b.) MH^+, 410.3484. $C_{22}H_{44}N_5O_2$ requires 410.3495]. ν_{max} 3300, 2950, 1670, 1630 cm^{-1}. λ_{max} (methanol) 219 nm (ε 31 000), $\lambda_{infl.}$ 208 nm. ^{1}H n.m.r. δ_H0.83, t, 3H; 1.24, bs, 18H; 1.78, s, 3H; 2.08, s, 3H; 2.30, bt, 2H; 3.50, bs, 8H; 5.69, s, 1H; 6.7-8.0, bd, 6H. ^{13}C n.m.r. δ_C14.4, 20.2, 27.7, 25.6, 27.4, 27.5, 29.4, 29.7, 31.9, 33.2, 33.8, 118.2, 152.4, 157.7, 168.2, 176.1.

N-(5-Guanidinopentyl)-3,3-dimethylacrylamide (237)

This acarnidine was prepared by the usual procedure (55%). [Found: (h.r.f.a.b.) MH^+, 227.1870. $C_{11}H_{23}N_4O$ requires 227.1872]. ν_{max} 3350, 2950, 1660, 1630 cm^{-1}. λ_{max} (ethanol) 220 nm (ε 27 000), λ_{max} (KOH, methanol) 219 nm (ε 12 000). ^1H n.m.r. δ_H 1.38, bs, 6H; 1.82, s, 3H; 2.05, s, 3H; 3.35, m (broad), 4H; 5.62, s, 1H; 6.6-8.0,(broad) 6H. ^{13}C n.m.r. δ_C (Me_2SO-d_6) 18.4, 22.7, 25.9, 27.2, 27.9, 37.8, 40.0, 118.3, 147.2, 155.8, 165.2.

N-(5-Guanidinopentyl)dodecanamide (238)

This acarnidine was prepared by the above procedure (45%). [Found: (h.r.f.a.b.) MH^+, 327.3129. $C_{18}H_{39}N_4O$ requires 327.3124]. ν_{max} 3300, 3200, 2950, 1670, 1630 cm^{-1}. λ_{max} 219 nm (ε 17 000). ^1H n.m.r. δ_H0.90, t, 3H; 1.15, s, 18H; 1.6, m (broad), 6H; 2.21, bs, 2H; 3.22, bs, 4H; 6.2-8.2, bd, 6H (exchanged by D_2O). ^{13}C n.m.r. δ_C14.0, 22.5, 23.8, 25.9, 29.2, 29.3, 29.5, 31.8, 36.7, 39.7, 42.1, 157.1, 174.7.

N-[3-(3,3-Dimethylacrylamido)propyl]-N-(6-dimethylpyrimidinohexyl)dodecanamide (156)

A solution of 10 mg (0.016 mmol) of the acarnidine (155), 4 mg (0.04 mmol) of 2,4-pentanedione, 3 mg (0.03 mmol) of sodium carbonate[7], 0.5 ml of water and 1 ml of ethanol were heated at reflux for 1.5 h. Extraction with ether (3 x 5 ml) followed by the usual work up yielded the dimethylpyrimidine (156) as an oil (9 mg, 100%). ^1H n.m.r. δ_H0.87, t, 3H; 1.27, s, 28H, 1.82, s, 3H; 2.13, s, 3H, 2.24, s, 6H;

3.3, m (broad), 8H; 5.00, bs, 1H; 5.50, s, 1H; 6.20, s, 1H; 6.65, bs, 1H. ^{13}C n.m.r. δ_C14.1, 19.7, 22.7, 23.9, 25.8, 26.7, 27.1, 27.4, 29.0, 29.4, 29.6, 32.0, 33.2, 35.2, 41.1, 42.1, 47.8, 109.6, 119.2, 150, 162.5, 167.2, 167.4, 174.0. Mass spectrum (e.i.) m/z 543 (7%, M^+); 431, (30, M-$C_6H_{10}NO$); 418 (8, M-$C_7H_{11}NO$); 416 (6, M-$C_7H_{13}N_0$); 360 (6, $C_{12}H_{23}O$); 192 (99, $C_{11}H_{18}N_3O$); 150 (45, $C_8H_{12}N_3O$); 136 (54, $C_7H_{10}N_3O$).

The freshly opened 2,4-pentanedione (Ajax) contained alkane and silicone impurities which complicated the initial analyses.

REFERENCES

1. Youngken, H.W.Jr., *Lloydia*, 1969, 32, 407.
2. der Marderosian, A., *J. Pharm. Sci.*, 1969, 58, 1.
3. The Roche Research Institute of Marine Pharmacology at Dee Why, Australia, recently closed because of the lack of commercially interesting chemicals isolated from marine sources.
4. Faulkner,D.J., *Tetrahedron*, 1977, 33, 1421.
5. Faulkner,D.J., and Fenical, W., (eds.), *"Marine Natural Products Chemistry"*, Plenum Press, New York, 1977.
6. Rinehart, K.L.Jr., Shaw, P.D., Shield, L.S., Gloer, J.B., Harbour, G.C., Koher, M.E.S., Samain, D., Schwartz, R.E., Tymiak, A.A., Weller, D.L., Carder, G.T., Munro, M.H.G., Hughes, R.G., Renis, H.E., Swyneberg, E.B., Stringfellow, D.E., Vavra, J.J., Coats, J.H., Zurenko, G.E., Kuentzel, S.L., Li, L.H., Bakus, G.J., Brusca, R.C., Craft, L.L., Young, D.N., and Connor, J.L., *Pure and Appl. Chem.*, 1981, 53, 795.
7. Carter, G.T. and Rinehart, K.L. Jr., *J.Am.Chem.Soc.*, 1978, 100, 4302.
8. Gottschalk, P., B.S. Thesis and research project, University of Illinois, Urbana, U.S.A., 1978.
9. Smith, P.A.S., *"Open Chain Nitrogen Compounds"*, Vol. I., Benjamin , New York, 1965, p.277.

10. Durant, G.J., Roe, A.M. and Green, A.L., "The Chemistry of Guanidines and their Actions at Adrenergic Nerve Endings". In *Progress in Medicinal Chemistry*, Vol. 7, part 1, Ellis, G.P., and West, G.B., (eds.), Butterworths, London, 1970, Chapter 3.

11. Harada, S., Muzata, E. and Kish, T., *Tetrahedron*, 1981, 37, 1317. Also see Hanada, K., Tamai, M., Morimoto, S., Adachi, T., Ogama, K. *Peptide Chem.*, 1979 (Pub. 1980), 17th 31; *Chem. Abst.* 1980, 93, 239854.

12. Chevolot, L., "Guanidine Derivatives", in *Marine Nature Products*, Vol. IV, Scheuer, P.J. (ed.), Academic Press, New York, 1981.

13. Harbour, G.C., Tymiak, A.A., Rinehart, K.L.Jr., Shaw, P.O., Hughes, R.G.Jr., Mizsak, S.A., Coats, J.H., Zurenko, G.E., Li, L.H. and Kuentzel, S.L., *J. Am. Chem. Soc.*, 1981, 103, 5604.

14. Walker, R.P., and Faulkner, D.J., *J. Am. Chem. Soc.*, 1981, 103, 6772.

15. Djura, P., and Faulkner, D.J., *J. Org. Chem.* 1980, 45, 735.

16. Wichmann, C.F., Boyer, G.L., Divan, C.L., Schantz, E.J. and Schoes, H.K., *Tetrahedron Lett.*, 1981, 22, 1941.

17. Three recent publications cite a number of interesting references; Yamamoto, H., and Maruoka, K., *J. Am. Chem. Soc.*, 1981, 103, 4186 and 6133; Bergeron, R.J., Burton, P.S., McGovern, K.A. and Klein, S.J. *Synthesis, 1981*, 732.

18. Barker, P.L., Gendler, P.L. and Rapoport, H., *J. Org. Chem.*, 1981, 46, 2455.

19. Hendrickson, J.B., Bergeron, R. and Sternbach, D.D., *Tetrahedron*, 1975, 31, 2517.

20. Nordlander, J.E., Catalane, D.B., Eberlein, T.H., Farkas, L.V., Howe, R.S., Stevens, R.M., Stansfield, R.E., Cox, J.L., Payne, M.J. and Vichbeck, A., *Tetrahedron Lett.*, 1978, 4987.

21.(a) Kenner, G.W., Moore, G.A., and Ramage, R., *Tetrahedron Lett.*, 1976, 3623;

(b) Coulton, S., Moore, G.A., and Ramage, R., *Tetrahedron Lett.*, 1976, 4005.

22. Zwierzak, A. and Podstawczyńska, I., *Angew. Chem. Int. Ed. Engl.*, 1977, 16, 702.

23. Moore, T.S., Boyle, M. and Thorn, V.M., *J. Chem. Soc.*, 1929, 39.

24. Sandler, S.R. and Karo, W., *Organic Functional Group Preparations*, Academic Press, New York, 1968, p.327.

25. Dixit, D.M. and Lenznoff, C.C., *J. Chem. Soc., Chem. Comm.*, 1977, 798.

26. Stahl, G.L., Walter, R. and Smith C.W., *J. Org. Chem.*, 1978, 43, 2285.

27. Barton, J.W., "Protection of N-H Bonds and NR_3". In, *Protective Groups in Organic Chemistry*, McOmie, J.F.W. (ed.), Plenum Press, London, 1973, chapter 2.

28. Gibson, M.S. and Bradshaw, R.W., *Angew. Chem. Int. Ed. Engl.*, 1968, 7, 919.

29. Elliot, J.D. and Jones, J.H., *J. Chem. Soc., Chem. Comm.*, 1977, 758.

30. Munro, A.M., *Chemistry and Industry*, 1964, 1806.

31. Mukaiyama, T., Tsuji, T. and Watanabe, Y., *Chemistry Lett.*, 1978, 1057.

32. Bannard, R.A., Casselman, A.A., Cockburn, W.F. and Brown, G.M., *Can. J. Chem.*, 1958, 36, 1541.

33. Short, J.H., Biermacher, U., Dunnigan, D.A. and Leth, T., *J. Med. Chem.*, 1963, 6, 275.

34. Jäger, G. and Geiger, R., *Chem. Ber.*, 1970, 103, 1727 and references sited within.

35. Nishimura, O., *Ger. Offen.*, 2528, 935., *Chem. Abstr.*, 1976, 84, 136056q.

36. Ramachandran, J. and Li, C.H., *J. Org. Chem.*, 1962, 27, 4006.

37. Bell, J.R., Jones, J.H., Regester, D.M. and Webb, T., *J.Chem.Soc., Perkin I*, 1974, 1961.

38. Jäger, G. and Geiger, R., *Liebigs. Ann. Chem.*, 1973, 1535 and 1928.

39. Fujino, M. and Shinagawa, S., *Chem. Pharm. Bull. Japan*, 1972, 20, 1016 and 1021.

40. Patthy, L. and Smith, E.L., *J. Biol. Chem.*, 1975, 250, 557.

41. Fujino, M., Nishimura, O., Wakismasu, M. and Kitada, C., *J. Chem. Soc., Chem. Comm.*, 1980, 668.

42. Horowitz, J.P. and Rila, C.C., *J. Am. Chem. Soc.*, 1958, 80, 431.

43. Tysee, D.A., Bauscher, L.P. and Haake, P., *J. Am. Chem. Soc.*, 1973, 95, 8066.

44. Nomenclature was based on *"Nomenclature of Organic Chemistry"*, IUPAC, Butterworth, London, 1969.

45. Olomucki, M. and Hebrard, P., *Tetrahedron Lett.*, 1969, 13.

46. Typical examples are the references quoted by Braun, C., *J. Chem. Ed.*, 1931, 8, 2175, and by Mull, R.P., and Maxwell, R.A. in *"Medicinal Chemistry"*, Vol. 7, Schlittler, E., (ed.), Academic Press, New York, 1967.

47. Sidhu, G.S., Thyagarajan, G. and Mazharuddin, M., *Indian J. Chem.*, 1964, 2, 170.

48. Khol´tsanfel´, Kh. and Rikhter, K., *Z. Obschei Khimii*, (Eng. Ed.), 1962, 32, 1337.

49. Scott, A.I., *"Interpretation of the Ultraviolet Spectra of Natural Products"*, Permagon Press, Oxford, 1964.

50. Salzburg, P.L. and Supniewski, J.V., *Organic Syn.*, Coll. Vol. I., Gillman, H., (ed.), J. Wiley and Sons, New York, 1932, p.119.

51. Kormendy, K. and Volford, J., *Acta. Chim. Acad. Si. Hung.*, 1962, 32, 121; *Chem. Abstr.* 1963, 58, 1444f.

52. Vogel, A.I. *"A Textbook of Practical Organic Chemistry including Qualitative Organic Analysis"*, Longmans, Green and Co., London, 3rd Edition, 1956, p.185.

53. Carter, H.E., Frank, R.L. and Johnston, H.W., *Organic Syn.*, Coll. Vol. III, Horning, E.C. (ed.), J. Wiley and Sons, New York, 1955, p.167.

54. Nagasawa, T., Kuroiwa, K., Narita, K. and Isowa, Y., *Bull. Chem. Soc. Japan*, 1973, 46, 1269.

55. Searles, S. and Nukina, S., *Chem. Rev.*, 1959, 59, 1077.

56. ElAmin, B., Anatharamaiah, G.M., Royer, G.P. and Means, G.E., *J. Org. Chem.*, 1979, 44, 3442.

57. Boissonas, R.A. "Selectively Removable Amino Protective Groups Used in the Synthesis of Peptides", in *Advances in Organic Chemistry*, Vol.3, Raphael, R.A., Taylor, E.C. and Wynberg, H.,(eds.), Interscience, New York, 1963, p.159ff.

58. Bruson, H.A. "Cyanoethylation". In *Organic Reactions*, Vol. 5, Adams, R. (ed.) John Wiley and Sons, New York, 1948, p.79.

59. Normant, H., *Angew. Chem. Int. Ed.*, 1967, 6, 1046.

60. Mowry, D.T., *Chem. Rev.*, 1948, 42,189, and Luten D.J., *J. Org. Chem.*, 1938, 3, 588.

61. Cheng, M.T., and Rinehart, K.L.Jr., *J. Am. Chem. Soc.*, 1978, 100, 7409.

62. Bald, E., Saigo, K. and Mukaiyama, T., *Chemistry Lett.*, 1975, 1163.

63. Hayakawa, T., Fujiwara, Y. and Noguchi, J. *Bull. Chem. Soc. Japan*, 1967, 40, 1205.

64. Lespagnol, A., Cuignet, E. and Debaert, M., *Bull. Soc. Chim. France*, 1960, 387.

65. Cox, E.H. and Sprague, J.M., *U.S. Patent* 2557633, *Chem. Abstr.*, 1952, 46, 1039g.

66. Ferris, A.F. and Schutz, B.A., *J. Org. Chem.*, 1963, 28, 71.

67. Wegner, M.M. and Rapoport, H., *J. Org. Chem.*, 1977, 42, 3065.

68. Barrett, A.G.M. and Lana, J.C.A., *J. Chem. Soc., Chem. Com.*, 1978, 471.

69. Golding, B.T., University of Warwick, England, 1982, personal communication.

70. Blunt, J.W., Munro, M.H.G. and Yorke, S.C., *Tetrahedron Lett.*, in press, 1982.

71. Schneider, W., Hoyer, J., Ehrenstein, W., Haller, R., Hansel, W. and Lehmann, K., "Amines". In *Methodicum Chimicum. C-N Compounds* (Vol.6), Korte, F. (ed.) Thieme, Stuttgart, 1975, p.439ff.

72. Layer, R.W., *Chem. Rev.*, 1963, 63, 489.

73. Malpass, J.R., "Aliphatic, Acyclic and Cyclic Amines". In *Comprehensive Organic Chemistry*, Vol. 2, Barton Sir D., and Ollis, W.D., (eds.), Pergamon Press, Oxford, 1979, part 6, p.1ff.

74. Emerson, W.S., "The Preparation of Amines by Reductive Alkylation". In *Organic Reactions*, Vol. 4., Adams, R., (ed.), Wiley, New York, 1948.

75. Carpino, L.A., *J. Am. Chem. Soc.*, 1957, 79, 98.

76. Djerrasi,C., Engle, R.R. and Bowers, A., *J. Org. Chem.*, 1956, 21, 1547.

77. Ratcliffe, R. and Rodihorst, R., *J. Org. Chem.*, 1970, 35, 4000.

78. Corey, E.J. and Suggs, J.W., *Tetrahedron Lett.*, 1975, 2647.

79. Cheng, Y.S., Liu, W.L. and Chen, S., *Synthesis*, 1980, 223.

80. Cardillo, G., Orena, M. and Sandri, S., *Synthesis*, 1976, 394.

81. Rao, Y.S. and Filler R., *J. Org. Chem.*, 1974, 39, 3304.

82. Sharpless, K.B. and Akashi, K., *J. Am. Chem. Soc.*, 1975, 97, 5928.

83. Kakis, F.J. Fetizon, M., Douchkine, N., Golfier, M., Mourges, P. and Prange, T., *J. Org. Chem.*, 1974, 39, 523.

84. Moffat, J.G., "Sulphoxide-Carbodiimide and Related Oxidations". In *Oxidation*, Vol. 2, Augustine, R.L. and Trecker, D.J., (eds.) Marcel Decker, New York, 1971, chapter 1.

85. Feiser, M. and Fieser, L.F., *Reagents for Organic Synthesis*, Vol. 2, Wiley-Interscience, 1969, p.162.

86. Parikh, J.R. and Doering, W. von E., *J. Am. Chem. Soc.*, 1967, 89, 5505.

87. Mancuso, A.J., Huang, S.L. and Swern, D., *J. Org. Chem.*, 1978, 43, 2480.

88. Corey, E.J. and Kim, C.W., *J. Org. Chem.*, 1973, 38, 1233.

89. Borch, R.F. and Hassid, A.I., *J. Org. Chem.*, 1972, 37, 1673.

90. Raber, D.J., Guida, W.C. and Schoenberger, D.C., *Tetrahedron Lett.*, 1981, 22, 5107.

91. Starr, D. and Hixon, R.M., *Org. Syntheses*, Coll. Vol.II, Blatt, A.H. (ed.), J. Wiley and Sons, 1943, p.571.

92. Sugiura, S., Inoue, S., Hayashi, Y., Kishi, Y. and Goto, T., *Tetrahedron*, 1969, 25, 5155.

93. Putokhin, N., *Trans. Inst. Pur Chem. Reagents (Moscow)*, 1927, 6, 10; *Chem. Abstr*, 1929, 23, 2938; *Chem. Ber.*, 1926, 59, 625.

94. Sheehan, J.C. and Bolhofer, U.A., *J. Am. Chem. Soc.*, 1950, 72, 2786.

95. Mizzoni, R.H., Hennessey, M.A. and Scholz, C.R. *J. Am. Chem. Soc.*, 1954, 76, 2414.

96. Hurd, C.D. and Saunders, W.H.Jr., *J. Am. Chem. Soc.*, 1952, 74, 5324.

97. *Carbon-13 NMR Spectral Data*, Bremser, W., Ernst, L., Franke, B., Gerhards, R., Hardt, A., (eds.), Verlag-Chemie, GmbH, Weinheim, W. Germany, 1981.

98. Sarneski, J.E., Suprenant, F.K., Mollen, F.K. and Reilly, C.N., *Anal. Chem.*, 1975, 47, 2116.

99. Kratos Data Sheet No. 138 (1981).

100. Fenselau, C., *Anal. Chem.*, 1982, 54, 105A.

101. Rinehart, K.L.Jr., personal communication.

102. Gordon, A.J. and Ford, R.A.,*"The Chemist's Companion"*, John Wiley and Sons, New York, 1972.

103. *CRC Handbook of Chromatography*, Zweig, G. and Sherma, J., (eds.). CRC Press, Cleveland, U.S.A., 1972.

104. *Dictionary of Organic Compounds*, 4th edition, Heilbron, Sir I., (ed.), Eyre and Spotswood Ltd., London, 1965.

105. Kornblum, N., Larson, H.O., Blackwood, R.K., Mooberry, D.D., Oliveto, E.P. and Graham, G.E. *J. Am. Chem. Soc.*, 1956, 78, 1497.

106. Shildneck, P.R. and Windus, W., *Org. Syntheses*, Coll. Vol. II, Blatt, A.H., (ed.), John Wiley and Sons, New York, 1943, p.411.

107. Smith, G. and Anzelmi,E., *J. Am. Chem. Soc.*, 1935, 57, 2730.

108. Jacobs, W.A. and Heidelberger, M., *Org. Syntheses*, Coll. Vol. I., Gillman, H., (ed.), 2nd edition, J. Wiley and Sons, New York, 1941, p.153.

109. Finan, P.A. and Fothergill, G.A., *J. Chem. Soc.*, 1962, 2824.

110. Reisner, P.B. and Horning, E.C., *Org. Syntheses*, Vol. 30, Cope, A.C. (ed.), John Wiley & Sons, New York, 1950, p.22.

111. *CRC Handbook of Chemistry and Physics*, 55th edition, Weast, R.C., (ed.), CRC Press, Cleveland, U.S.A., 1974.

112. *The Merck Index*, 7th edition, Stecher, P.G., (ed.), Merck and Co., New Jersey, U.S.A., 1960.

113. Bohlmann, F., Zeisberg, R. and Klein, E., *Org. Magn. Reson.*, 1975, 7, 426.

114. Hunt, R., McOmie, J. and Sayer E.R.,*J.Chem.Soc.*, 1959, 525.

115. Hartung, W.H. and Simonoff, R., "Hydrogenolysis of Benzyl Groups". In *Organic Reactions*, Vol.7, Adams, R., (ed.), John Wiley and Sons, New York, 1953, p.263.

116. Zervas, L. and Theodoropoulos, D.M., *J. Am. Chem. Soc.*, 1956, 78, 1359; and Billimoria, J.D., and Lewis, J.O., *J. Chem. Soc. (C)*, 1968, 1404.

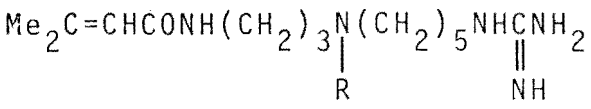
117. McAllen, D.T., Cullum, T.V., Dean, R.A. and Fidler, F.A., *J. Am. Chem. Soc.*, 1951, 73, 3627.

118. Baldwin, A.W., *J. Chem. Soc.*, 1929, 2963.

119. *Beilstein*, 1942, E II 4, 708.

120. *ibid*, 1929, IV, 421.

121. Berdy, J., "Research and Classification of Antibiotics," in *Advances of Applied Microbiology*, Perlman, D., (ed.), Academic Press, New York, 1974.

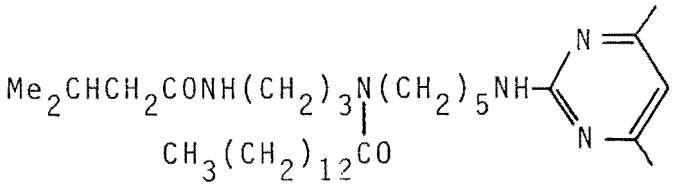


(1a-c)

1a, R = - $CO(CH_2)_{10}CH_3$

1b, R = - $CO(CH_2)_3CH{=}CH(CH_2)_5CH_3$ (Z)

1c, R = - $CO(CH_2)_2CH{=}CH(CH_2)_2CH{=}CHCH_2CH{=}CHCH_2CH_3$ (all Z)



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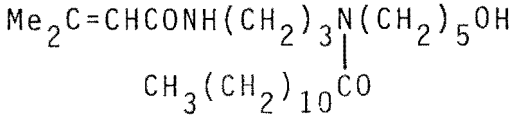

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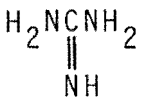

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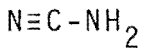

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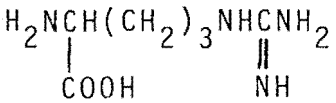
(6)



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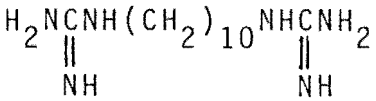

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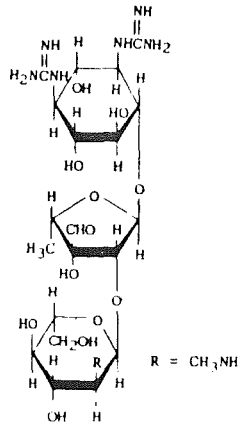

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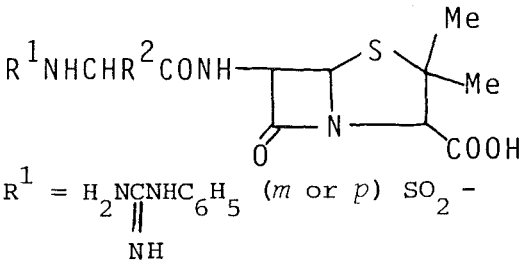
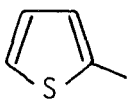


R^1 = $H_2NCNHC_6H_5$ (*m* or *p*) SO_2 -
NH

R^2 = C_6H_5 - or 

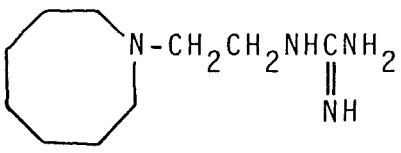
(10)

$H_2NCNH(CH_2)_nCOOR$
NH

(a) n = 1 - 5, R = H

(b) n = 2 - 8, R = C_7 - C_{12}

(11)



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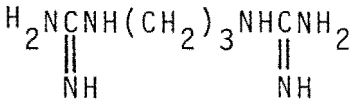

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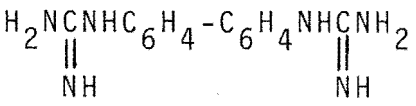

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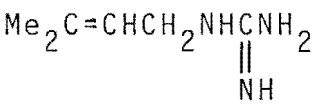
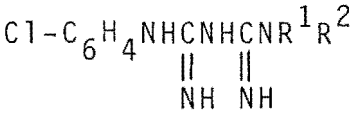
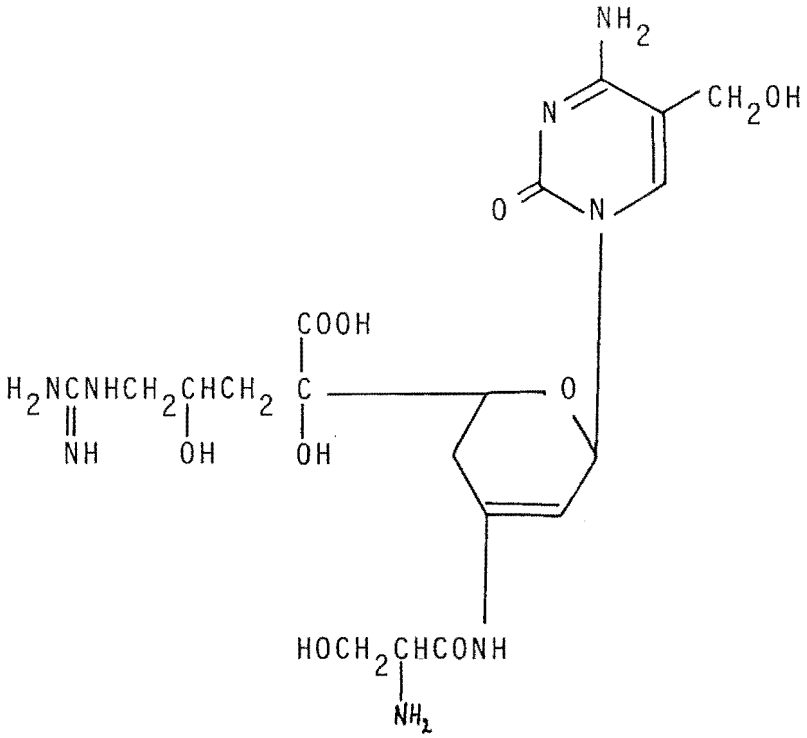


(15)



R^1 and R^2 are short alkyl chains.

(16)



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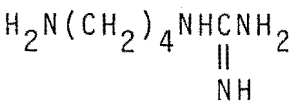

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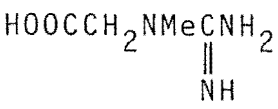

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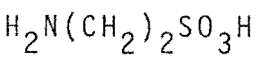

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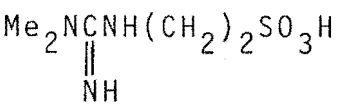

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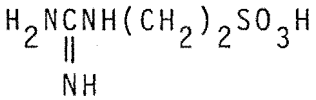

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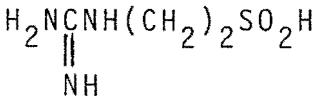

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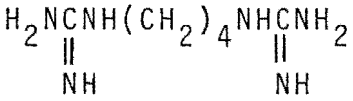

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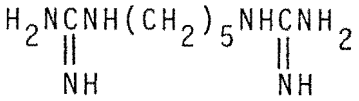

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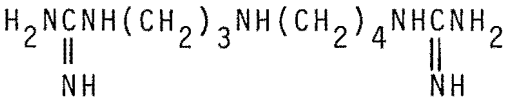

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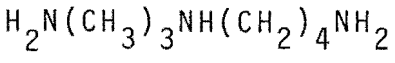

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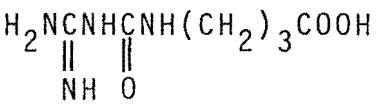

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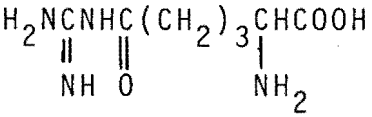

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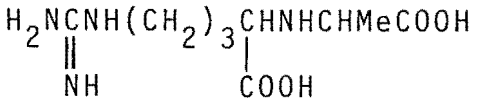

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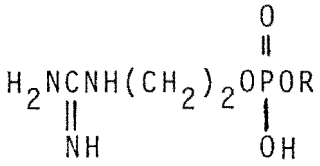
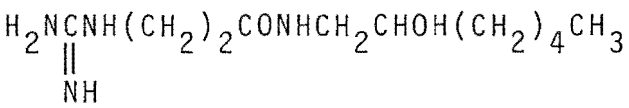


(31a-c)

31a, R = - $CH_2CH(NH_2)COOH$

31b, R = - Me

31c, R = - $CH_2CH(NMe_2)COOH$



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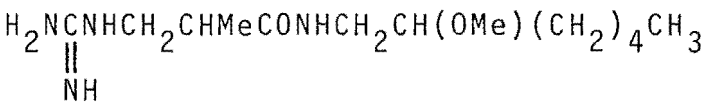

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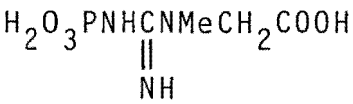

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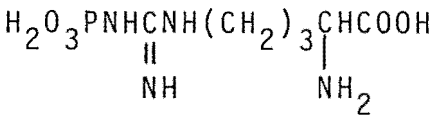
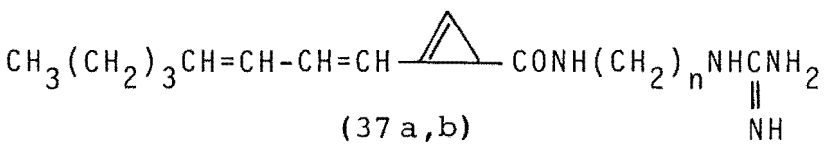


(35)

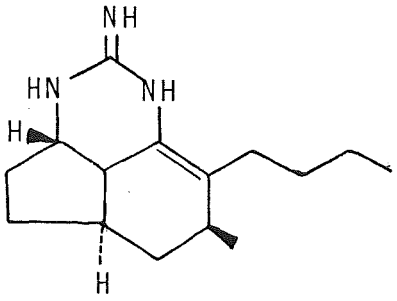
(36)



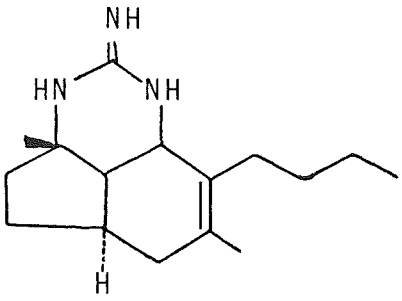
(37 a,b)

37a, n = 4

37b, n = 5



(38)



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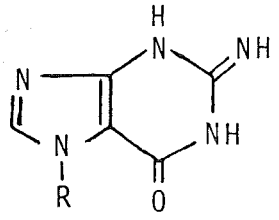
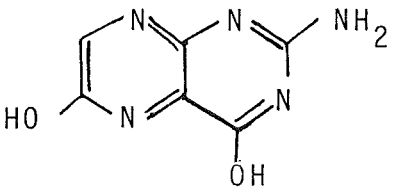


(40)

40a, R = H

40b, R = ribose



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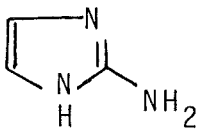

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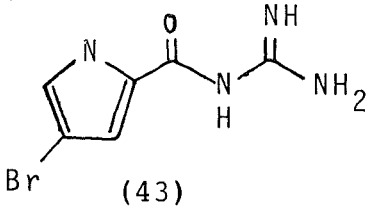

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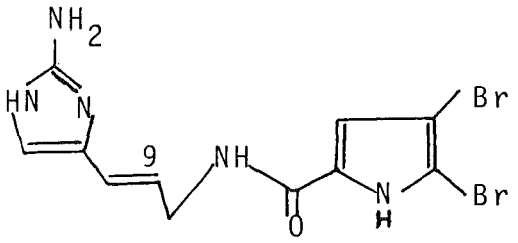

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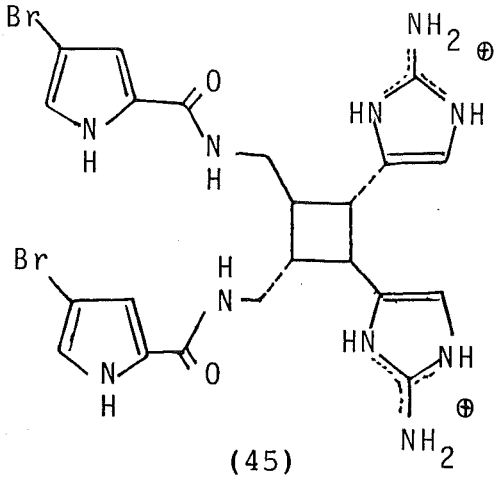

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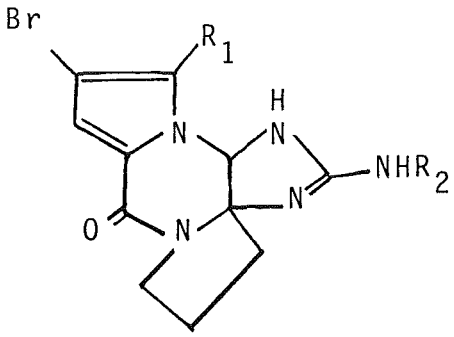
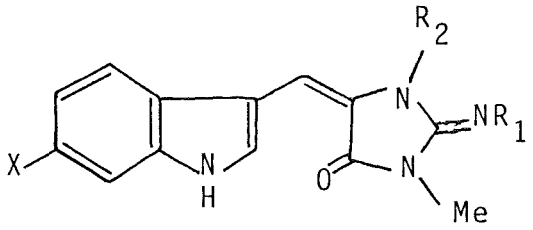


(46, a-c)

46a, $R_1=R_2=H$

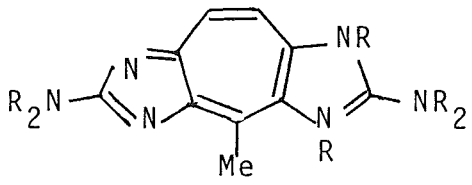
46b, $R_1=Br; R_2=H$

46c, $R_1=Br; R_2=-COCH_3$



(47)

	R_1	R_2	X
47a,	H	Me	H
47b,	Me	Me	H
47c,	H	H	H
47d,	H	H	Br



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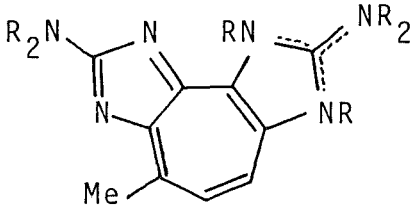

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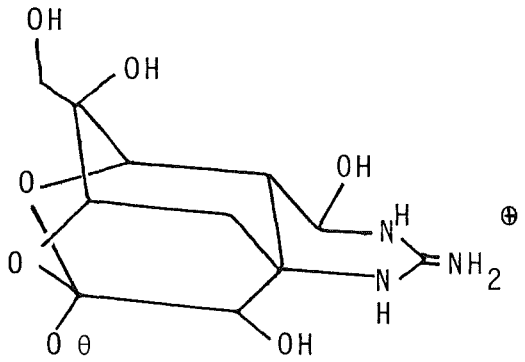

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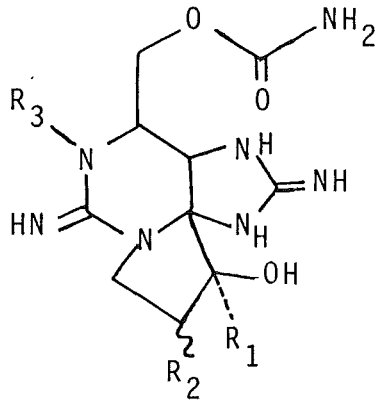

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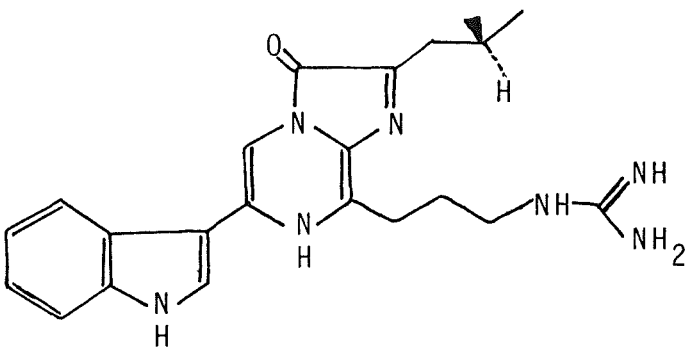

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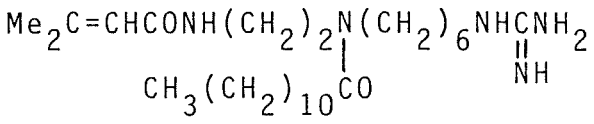

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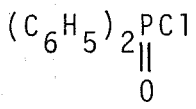

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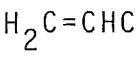

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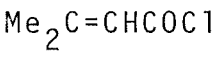

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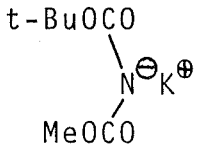

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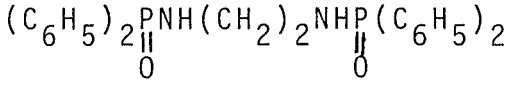

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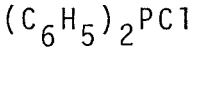

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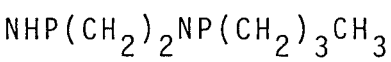

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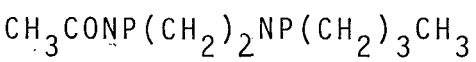

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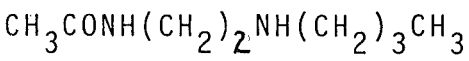

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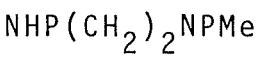

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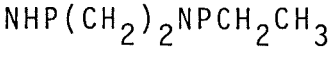

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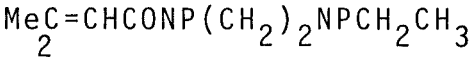

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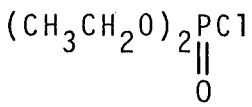

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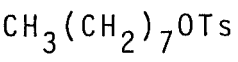

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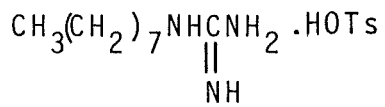

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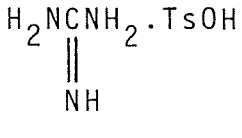

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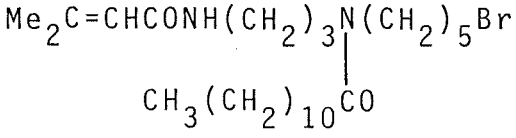

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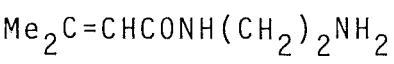

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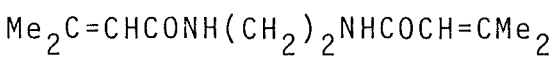

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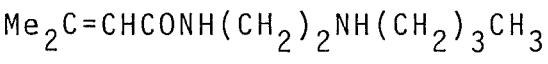

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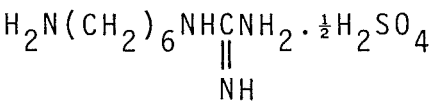

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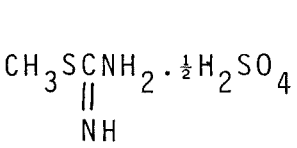

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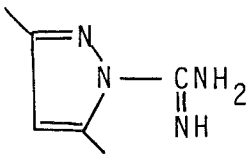

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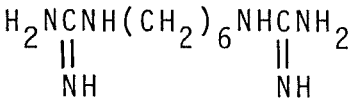
(77)



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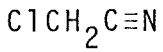

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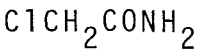

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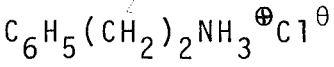

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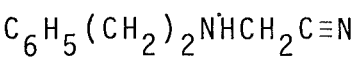

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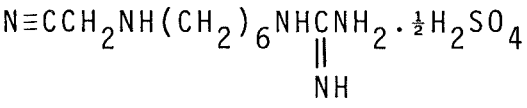

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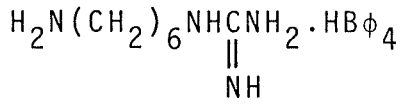

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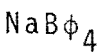

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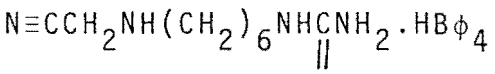

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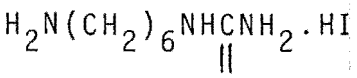

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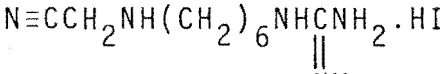

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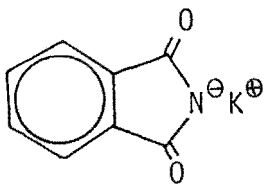

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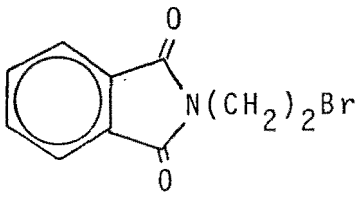
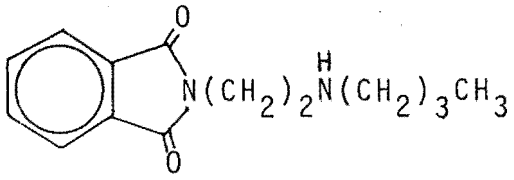
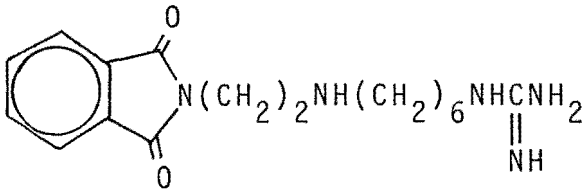


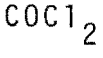
(90)



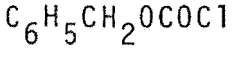
(91)



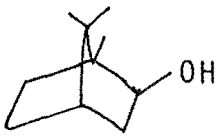
(92)



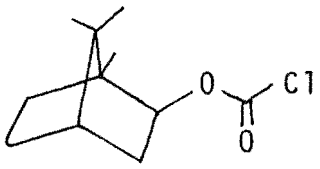
(93)



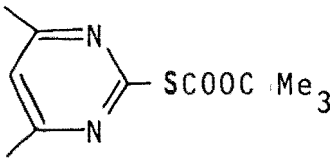
(94)



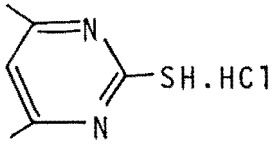
(95)



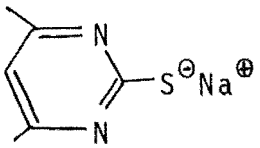
(96)



(97)



(98)



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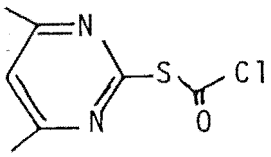
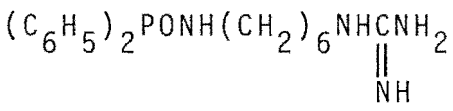
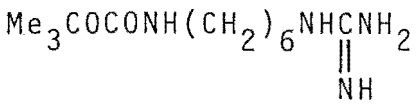


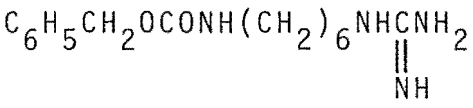
(100)



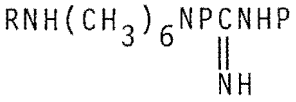
(101)



(102)



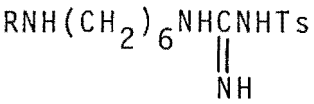
(103)



(104) R=$C_6H_5CH_2OCO$-; P=isobornyloxycarbonyl-

(105) R=H; P=isobornyloxycarbonyl-

(106) R=$C_6H_5CH_2OCO$-; P=H-

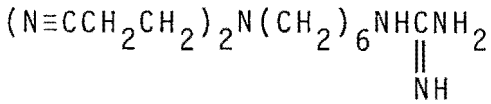


(107) R=$C_6H_5CH_2OCO$-

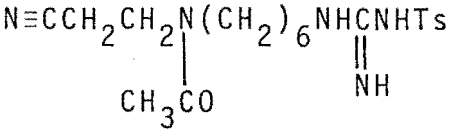
(108) R=H

(109) R=N≡CCH_2CH_2-

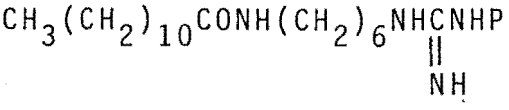
(110) R=N≡CCH_2-



(111)



(112)

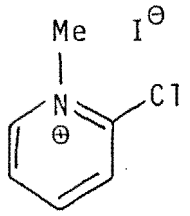


(114) P=H

(115) P=Ts

$CH_3(CH_2)_{10}COCl$

(113)



(116)

$H_2N(CH_2)_6NHC(=NH)NHNO_2$

(117)

$N{\equiv}CCH_2NH(CH_2)_6NH_2$

(118)

$CH_3SC(=NH)NH_2.HI$

(119)

$CH_3SC(=NH)NHTs$

(120)

$CH_3SC(=NTs)SCH_3$

(121)

$CH_3SC(=NTs)Cl$

(122)

$(C_6H_5)_3CCl$

(123)

$PNH(CH_2)_6NHP'$

(124) $P=P'=(C_6H_5)_2PO-$

(125) $P=P'=(CH_3CH_2O)_2PO-$

(126) $P=(C_6H_5)_2PO-$; $P'=H$

(127) $P=(CH_3CH_2O)_2PO-$; $P'=H$

(128) $P=P'=(C_6H_5)_3C-$.

(129) $P=(C_6H_5)_3C-$; $P'=H$

(130) $P=(C_6H_5)_3C-$; $P'= -CH_2C{\equiv}N$

$PNH(CH_2)_6NHP'$

(131) $P=Me_3COCO-$; $P'= H$

(132) $P=P'=C_6H_5CH_2OCO-$

(133) $P=C_6H_5CH_2OCO-$; $P'=H$

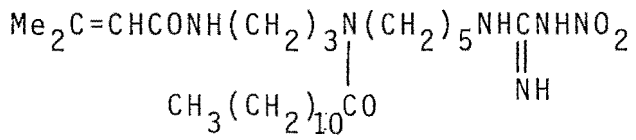
$C_6H_5CH_2OCONH(CH_2)_2NH_2$

(134)

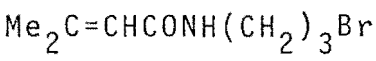
$RNH(CH_2)_6NHCOOCMe_3$

(135) $R=N{\equiv}CCH_2-$

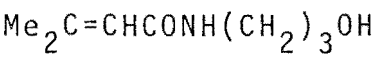
(136) $R=N{\equiv}C(CH_2)_2-$



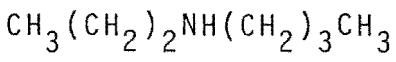
(137)



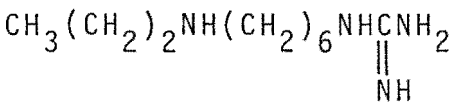
(138)



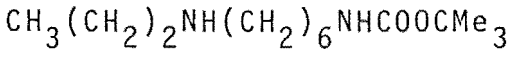
(139)



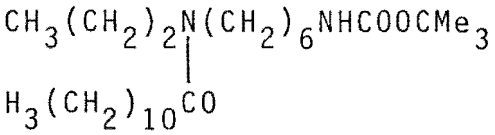
(140)



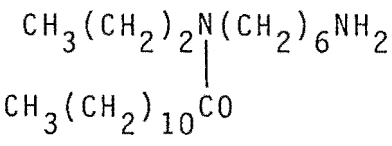
(141)



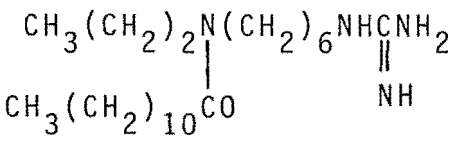
(142)



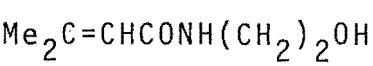
(143)



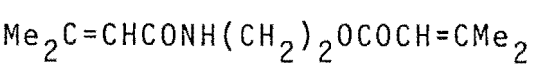
(144)



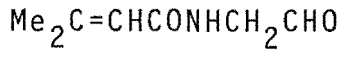
(145)



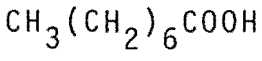
(146)



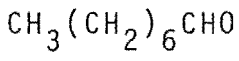
(147)



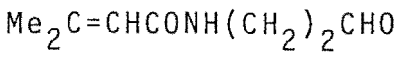
(148)



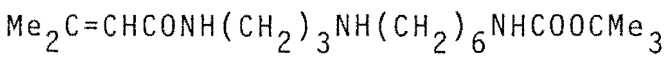
(149)



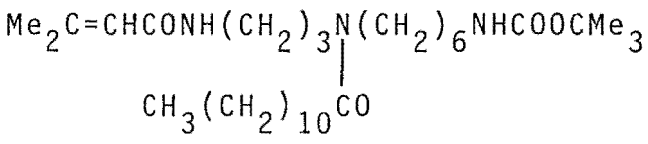
(150)



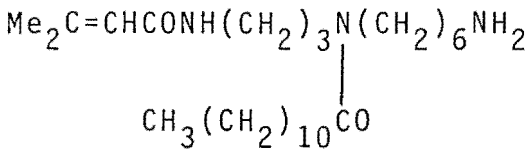
(151)



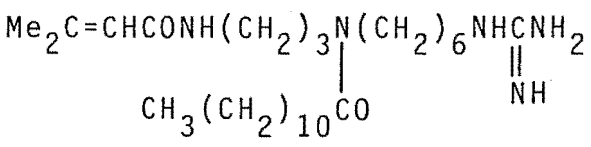
(152)



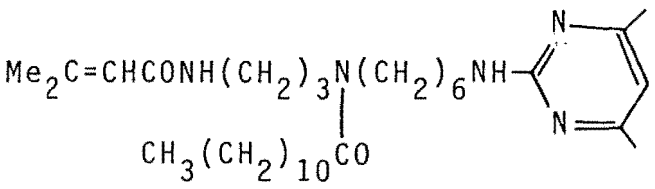
(153)



(154)



(155)



(156)

$CH_3(CH_2)_{16}COCl$

(157)

$CH_3(CH_2)_7CH{=}CH(CH_2)_7COCl(Z)$

(158)

$H_2N(CH_2)_4OH$

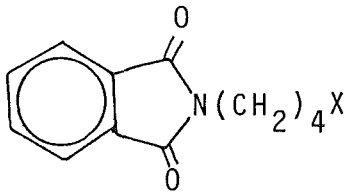
(159)

$H_2N(CH_2)_5NH_2$

(160)

$Cl(CH_2)_4OH$

(161)



(162) X=OH

(163) X=Br

$Me_2C{=}CHCONH(CH_2)_xOH$

(164) x=4

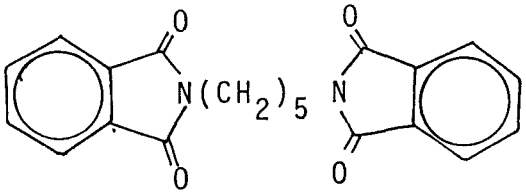
(165) x=5

$Me_2C{=}CHCONHCH_2CH(OMe)_2$

(166)

$H_2NCH_2CH(OMe)_2$

(167)



(168)

$H_2N(CH_2)_yNHCOOCMe_3$

(169) y=5

(170) y=4

(171) y=2

$Me_2C{=}CHCONHCH_2CH{=}N(CH_2)_6NHCOOCMe_3$

(172)

$Me_2C{=}CHCONH(CH_2)_xCHO$

(173) x=4

(174) x=3

$Me_2C=CHCONH(CH_2)_xNH(CH_2)_yNHCOOCMe_3$

	x	y
(175)	3	5
(176)	3	4
(177)	3	2
(178)	5	5
(179)	5	2
(180)	2	5
(181)	2	2

$Me_2C=CHCONH(CH_2)_xNR(CH_2)_yNHCOOCMe_3$

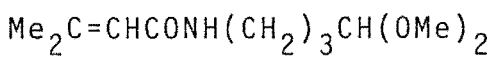
	x	y	R
(182)	3	6	18.0
(183)	3	6	18:1ω9
(184)	3	5	2.0
(185)	3	5	12.0
(186)	3	5	18.0
(187)	3	5	18:1ω9
(188)	3	4	12.0
(189)	3	4	18.0
(190)	3	4	18:1ω9
(191)	3	2	12.0
(192)	3	2	18.0
(193)	3	2	19:1ω9
(194)	5	5	12.0
(195)	5	2	12.0
(196)	2	5	12.0
(197)	2	2	2.0
(198)	2	2	12.0

$Me_2C=CHCONH(CH_2)_xNR(CH_2)_yNHR'$

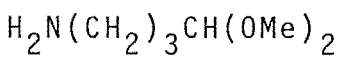
R'=H	x	y	R	R'= $-C(=NH)NH_2$
(199)	3	6	18.0	(216)
(200)	3	6	18:1ω9	(217)
(201)	3	5	2.0	(218)
(202)	3	5	12.0	(219)
(203)	3	5	18.0	(220)
(204)	3	5	18:1ω9	(221)
(205)	3	4	12.0	(222)
(206)	3	4	18.0	(223)
(207)	3	4	18:1ω9	(224)
(208)	3	2	12.0	(225)
(209)	3	2	18.0	(226)
(210)	3	2	18:1ω9	(227)
(211)	5	5	12.0	(228)
(212)	5	2	12.0	(229)
(213)	2	5	12.0	(230)
(214)	2	2	2.0	(231)
(215)	2	2	12.0	(232)

$RNH(CH_2)_5NHR'$

	R	R'
(233)	$Me_2C=CHCO-$	$-COOCMe_3$
(234)	$CH_3(CH_2)_{10}CO-$	$-COOCMe_3$
(235)	$Me_2C=CHCO-$	H
(236)	$CH_3(CH_2)_{10}CO-$	H
(237)	$Me_2C=CHCO-$	$-C(=NH)NH_2$
(238)	$CH_3(CH_2)_{10}CO-$	$-C(=NH)NH_2$



(239)



(240)